Glaucoma medication: evidence from clinical trials and effects in practice

GLAUCOMA MEDICATION

EVIDENCE FROM CLINICAL TRIALS AND EFFECTS IN PRACTICE

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EVIDENCE FROM CLINICAL TRIALS AND EFFECTS IN PRACTICE

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Contents

Abbreviations

ALT	Argon laser trabeculoplasty
bid	Twice daily
CI	Confidence interval
DURING	Dutch research project on treatment outcome in glaucoma patients
EGS	European glaucoma society
ICD-9	International classification of diseases-9
IOP	Intraocular pressure
LTP	Laser trabeculoplasty
MeSH	Medical subject heading
mmHg	Millimeters of mercury
NPG	Normal pressure glaucoma
OAG	Open-angle glaucoma
OH	Ocular hypertension
POAG	Primary open-angle glaucoma
POAG suspect	Primary open-angle glaucoma suspect
RCT	Randomized Clinical Trial
SD	Standard deviation
SE	Standard error of the mean
Target IOP	*Target intraocular pressure*
tid	Three times daily
qd	Once daily

1

Introduction

Epidemiology of glaucoma

Glaucoma is a chronic progressive optic neuropathic disorder of the eye. Glaucoma leads to loss of optic nerve tissue, resulting in visual field loss, and eventually blindness.[1, 2] Worldwide, glaucoma is the third leading cause of blindness.[3] In 2000 it was estimated that 67 million persons were affected by glaucoma, of whom 6.7 million people were bilaterally blind.[4] Estimations of the incidence of glaucoma vary between populations.[4] In a Barbadian population 4-year incidences of open-angle glaucoma were 1.2% at ages 40-49 years, 1.5% at ages 50-59 years, 3.2% at ages 60-69 years and 4.2% in patients aged over 70 years.[5] In European populations these incidences are lower and the disease occurs later in life.[6-8] In Europeans aged 70 years and over, the incidence raises exponentially compared with Europeans aged under 70 years.[4] Klein et al. found a prevalence of 4.7% in Caucasians aged 75 years and over.[9] In the Netherlands a study based on registrations in general practices showed an incidence of 5300 new glaucoma patients per year for men and 6800 for women and a prevalence of 36,300 for men and 49,200 for women.[10]

Risk factors for glaucoma

Risk factors for glaucoma can be divided into definite and possible risk factors. The most important risk factor for glaucoma is an increased intraocular pressure (IOP).[11-17] Other definite risk factors for glaucoma are increasing age,[18, 19] a positive family history of glaucoma,[18-21] and ethnicity.[6, 22] Less convincing evidence is found for myopia,[23] and diabetes mellitus.[19, 24-26] It has not yet been established whether cardiovascular disease,[18, 19, 27] and disorders of the blood flow in the optic nerve,[28, 29] increase the risk for glaucoma.

The mean IOP in the general population is approximately 16 mmHg with a standard deviation of 2.5 mmHg.[3, 30] IOP has a non-Gaussian distribution, skewed towards higher pressures, especially in individuals over age 40. The range of normal IOP has been defined as approximately 10-21 mmHg.[3] IOP is the result of the equilibrium of the production and outflow of aqueous humour. The aqueous humour leaves the eye through the trabecular meshwork and via uveoscleral outflow. The trabecular meshwork is a sieve-like structure that is situated in the anterior chamber angle between the iris and the cornea. After passing the trabecular meshwork aqueous humour flows through Schlemm's canal to the episcleral veins from where it is drained away. In the uveoscleral route, the aqueous humour passes across the ciliary body into the suprachoroidal space and is drained by the venous circulation in the ciliary body, choroid and sclera (figure 1).

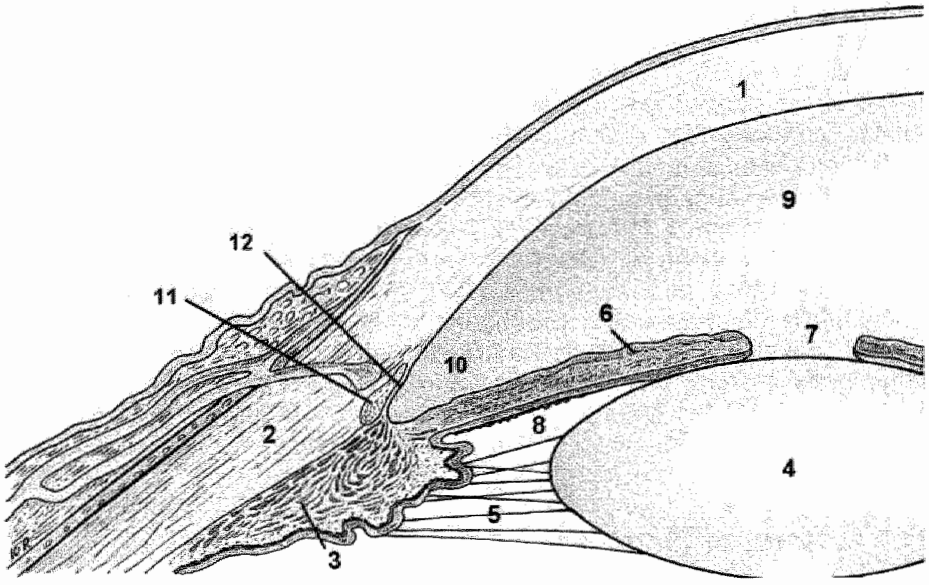

Figure 1. Anterior segment of the eye. 1. Cornea; 2. Sclera; 3. Ciliary body; 4. Lens; 5. Zonular fibres; 6. Iris; 7. Pupil; 8. Posterior chamber; 9. Anterior chamber; 10. Anterior chamber angle; 11. Schlemm's canal; 12. Trabecular meshwork
(adapted from Stilma JS, Voorn ThB (red.), Oogheelkunde, series Praktische Huisartsgeneeskunde, Bohn Stafleu van Loghum, Houten 2002, with permission)

Intraocular pressure varies with a number of factors, including the following:[3]

- Time of day
- Heartbeat
- Respiration
- Exercise
- Fluid intake
- Systemic medication
- Ocular medication

The amplitude of the intraocular pulse varies from 0 mmHg to over 6 mmHg, with mean values of 1.5 to 2.5 mmHg.[31, 32] Glaucomatous eyes have a significantly greater range in diurnal variation of IOP.[33, 34] A large diurnal variation may be a prognostic factor for visual field loss.[35] Hence, the IOP varies not only diurnally, but also within minutes and seconds.

Classification

Based on the width of the anterior chamber angle, glaucoma is generally classified into open-angle and angle-closure glaucoma. The mechanism of aqueous outflow impairment, and hence also the pathologic mechanism differs between those types of glaucoma.

In this thesis results of studies performed in primary open-angle glaucoma (POAG), primary open-angle glaucoma suspect (POAG suspect), normal pressure glaucoma (NPG) and ocular hypertension (OH) are discussed. Primary glaucomas are not associated with known ocular or systemic disorders that cause increased resistance to aqueous outflow. The primary glaucomas usually affect both eyes and may be inherited.[3] Other glaucomas such as angle closure glaucoma or secondary open-angle glaucoma are not discussed. In a general population the number of glaucoma patients diagnosed with POAG (suspect), NPG or OH exceeds other types of glaucoma in prevalence by over ten-fold.

Primary open-angle glaucoma (suspect), normal pressure glaucoma, and ocular hypertension occur in eyes with open anterior chamber angles (figure 1). The mechanism of increased resistance to aqueous outflow as it occurs in open-angle glaucoma is a direct alteration in the structures involved with aqueous drainage: trabecular meshwork and Schlemms canal (figure 1).

Diagnosis

The diagnosis primary open-angle glaucoma is made if the eye has a normal-appearing, open anterior-chamber angle and two or more of the following findings:[3]

- Appearance of the optic disc or retinal fiber layer that is suggestive of glaucomatous damage.
- Visual fields suspicious for early glaucomatous damage.
- An IOP consistently larger than 22 mmHg.

If only the optic disc or the visual field are suspicious for glaucomatous damage, the diagnosis primary open-angle glaucoma suspect is made. The presence of risk factors supports the diagnosis of primary open-angle glaucoma.

If optic nerve damage and visual field loss are present, but the IOP is below 21 mmHg, a patient has normal pressure glaucoma. When an elevated IOP is measured on consecutive measurements, but glaucomatous nerve head changes and visual field loss are absent, the condition is termed ocular hypertension.

Clinical evaluation

POAG (suspect), NPG or OH assessment involves a study of: the IOP, optic nerve, visual field and the drainage angle of the eye. This is performed by tonometry, funduscopy, perimetry and gonioscopy respectively.

Tonometry

IOP is measured by relating a deformation of the globe to the force responsible for the deformation. The most accurate technique for measuring the IOP is Goldmann applanation tonometry.[36] Other examples of tonometers are non-contact tonometers, the Schiøtz tonometer, the Perkins tonometer and the Tonopen.

Before conducting applanation tonometry, the cornea is first anaesthetized. Subsequently, a plastic biprism mounted on a standard split lamp is used to applanate the cornea (figure 2). The examiners' view is directed through the centre of the biprism. Two beam-splitting prisms within the applanating unit optically convert the circular area of corneal contact into semicircles. The prisms are adjusted so that the inner margins of the semicircles overlap when 3.06 mm of cornea is applanated.[30]

The Goldmann applanation tonometer is considered the gold standard. The reliability of measurements depends, however, on the reliability of its operator.[36] Compared to less experienced operators, experienced operators produce the lowest intra-observer variation.[37] Dielemans et al, found a mean intra-observer variation for the first measurement of 1.64 (SD 2.07) mmHg and mean inter-observation values were 1.79 (SD 2.41) mmHg.[36] Based on several studies Whitacre and Stein report error ranged from –3 to + 3 mmHg, because of inter-observer variability.[31] Both the intra- and inter-observer variation are reduced when 3 measurements are averaged together. For this reason it is recommended that a minimum of 3 readings within 3 mmHg is taken, and the averaged value is recorded as IOP.[38]

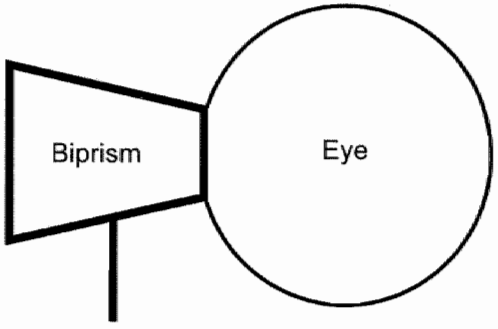

Figure 2. Applanation tonometry

Sources of error with Goldmann applanation tonometry

Instrumental

The semicircles, the width of the meniscus may influence the reading slightly with wider menisci falsely causing higher pressure estimates. Improper vertical alignment (one semicircle larger than the other) will also lead to a falsely high IOP estimate.[30] In addition, an improperly calibrated Goldmann tonometer can be a source of error.[30]

Eyes

The thickness of the cornea has been shown to influence the pressure estimate, with thin corneas producing falsely low readings.[39, 40] A thick cornea causes a falsely high measurement if the thickness is due to increased collagen fibrils, whereas low readings occur if thickness is due to edema.[30] Corneal curvature and has also been shown to influence IOP measurements.[41] An irregular cornea will also distort the semicircles and interfere with the accuracy of the IOP estimates. Contact of the biprism with the cornea causes an apparent decrease in IOP over a period of minutes,[31] and prolonged contact leads to injury of the cornea.

Physical appearance

Some studies found a positive association between high body mass index and POAG,[19, 42] where others found no association.[43] The difference may be explained by the instrument used for the IOP measurement. Dos Santos et al found that in obese patients the mean IOP measured by Goldmann tonometer is significantly higher than when measured by Perkins tonometer (20.9 mmHg vs. 16.3 mmHg), while in the control group no differences were found. These authors conclude that in obesity simultaneously breath-holding and thorax compression may a causative factor for transitory elevations of IOP.[44]

Funduscopy

Through an aperture in the sclera (scleral canal) the optic nerve leaves the eye (figure 3). This optic nerve consists of a variable number of optic nerve fibers (600.000-1.400.000) which originate in the retinal nerve fiber layer. The entrance of the nerve fibers into the optic nerve is known as the optic nerve head which consists of neural tissue (the neuroretinal rim) and a central depression, lacking neural tissue (the cup). The size of the cup is related to the diameter of the disc. The proportion between the cup and the disc is expressed as cup/disc ratio (figure 4).

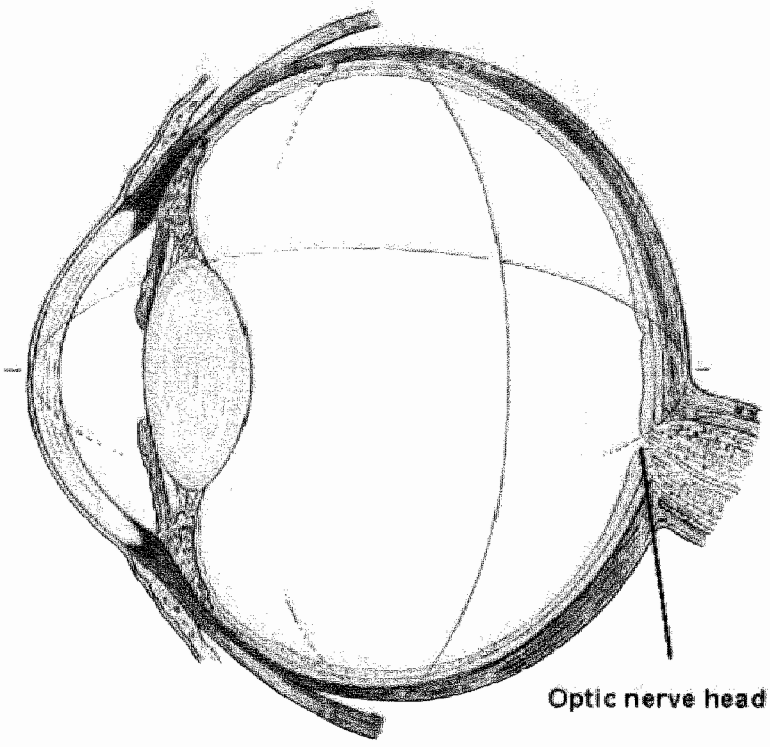

Figure 3. Section of the eye, with optic nerve head
(adapted from Stilma JS, Voorn ThB (red.), Oogheelkunde, series Praktische Huisartsgeneeskunde, Bohn Stafleu van Loghum, Houten 2002, with permission)

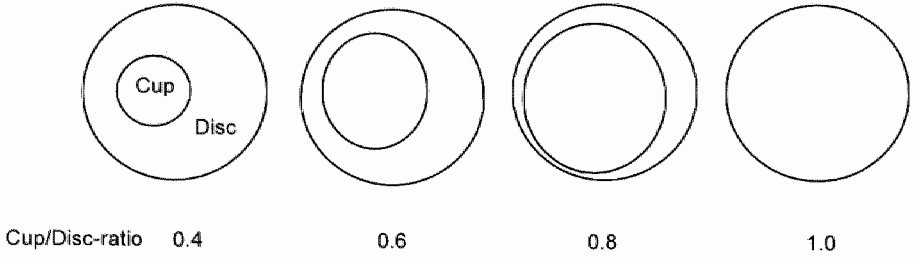

Figure 4. Cup/disc ratio

Elevated IOP can lead to death of optic nerve fibres, resulting in a narrowing of the neuroretinal rim and consequently to an enlargement of the cup. Since larger cup/disc ratios are an indicator of loss of optic nerve fibres, the cup/disc ratio has diagnostic value. In normal eyes the mean cup-disc ratio is 0.4, only 5% have a ratio greater than 0.7.[45] Even when no clinical signs of visual field loss are present, changes in cup/disc ratio may be an indication of glaucoma, since the changes in the optic nerve precede loss of visual field.[46] By funduscopy the ophthalmologist examines the optic nerve head, and can make an estimation of the cup/disc ratio.

Perimetry

Perimetry is used for detection and quantification of visual field defects. This examination is of major importance in the diagnosis of glaucoma; perimetry can be manual, semi- or full automatic. Static automated perimetry is the most sensitive technique of perimetry, and is available to most clinicians and researchers.[47] Manual perimetry is less accurate and less informative, but cheaper.[30]

In static perimetry it is tested which threshold of light intensity (brightness) a person can see on different locations in the visual field. These threshold intensities are compared with the intensities seen by persons of the same age. The intensities which can be seen are registered and mapped on the output (figure 5). Furthermore, the chance that the measured values are within the normal range is calculated. On the output can be seen in which areas decreased visual acuity is present. By comparing the present perimeter outputs with outputs from earlier visits, the ophthalmologist can determine whether progression of visual field loss has occurred.[48] Perimeters can be programmed to only test a certain part of the visual field (number of degrees of the visual field). Commonly used perimeters are the Humphrey visual field analyzer® and the Octopus®.

The most important variables in perimetry are: patient, perimetrist, fixation of the eye, background luminance, size of stimulus, luminance of stimulus, patient refraction, presentation time and the speed of stimulus movement.[49]

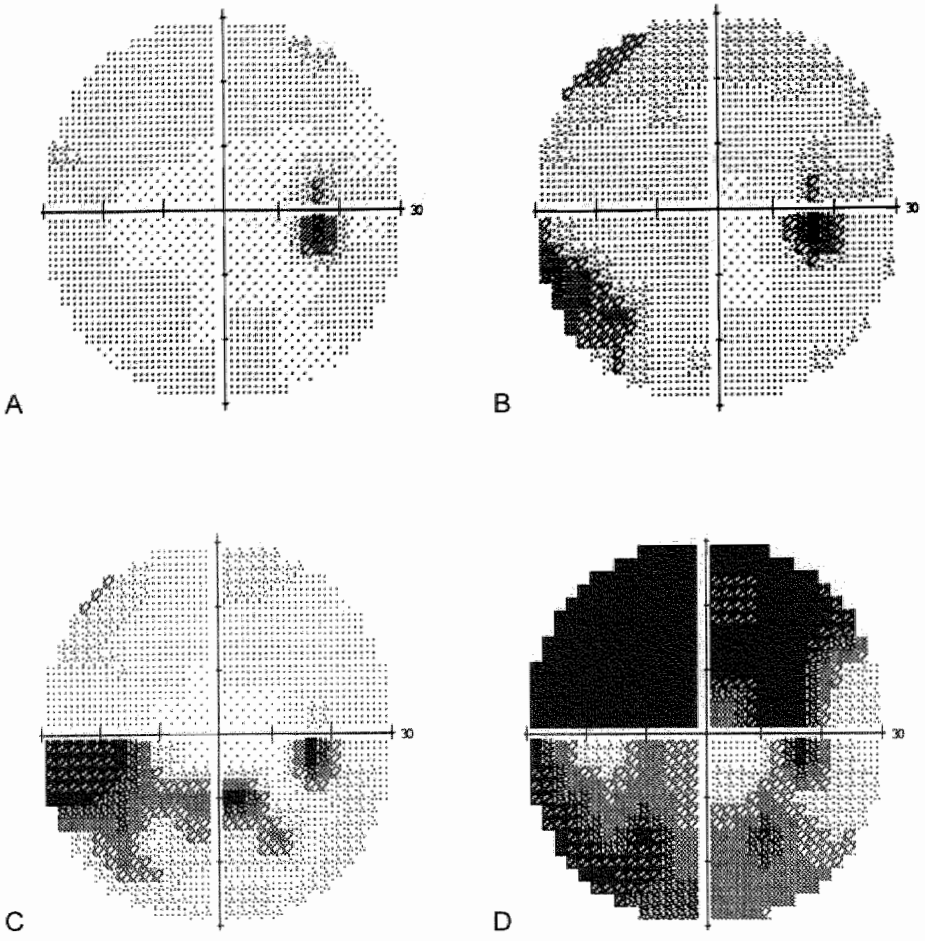

Figure 5. Humphrey visual field tests: A. No glaucomatous damage; B. Early glaucomatous damage; C. Moderate glaucomatous damage; D. Advanced glaucomatous damage

Gonioscopy

Gonioscopy is a technique used to examine structures in the anterior chamber angle. In the management of glaucoma, gonioscopic assessment is necessary to establish the type of glaucoma. Gonioscopy can be either direct or indirect. In both techniques, the examiner scans 360° of the anterior chamber angle. When performing direct gonioscopy, after application of a topical anaesthetic, the goniolens is positioned on the cornea. When performing indirect gonioscopy, the anterior chamber angle is examined by use of a gonioprism containing mirrors.

Treatment

Glaucoma treatment mainly involves lowering of the IOP. Concepts like improvement of ocular bloodflow, and direct neuroprotection might be other potential treatment options, however, these have not been proven. Therefore we focus on IOP lowering as treatment for glaucoma. Before starting treatment in an individual patient a target intraocular pressure (target IOP) is determined. Target IOP is an estimate of the IOP obtained with treatment that is expected to prevent further glaucomatous damage.[50] Target IOP varies between individuals according to:[50]

- IOP level before treatment
- The overall risk of IOP-related optic nerve damage
- Stage of glaucoma
- Rate of progression of glaucomatous damage
- Age of the patient
- Life expectancy of the patient
- Presence of other risk factors

Reduction of the IOP is possible by inhibiting the production of aqueous humour and/or improving the outflow. This can be achieved medically, by laser treatment or by surgery.

Ocular hypertension is not treated unless other risk factors for developing POAG are present. In patients with risk factors, the chance of developing open-angle glaucoma is over 1% per year. When nerve fiber layer defects or changes in cup/disc ratio occur, treatment is the same as in open-angle glaucoma. Also when the IOP frequently exceeds 30 mmHg treatment is initiated. The Ocular Hypertension Treatment Study found that in a five-year period less ocular hypertension patients converted to POAG in the group that received glaucoma treatment compared to the group without treatment.[11] Although 90% of the patients did not convert to POAG in five years, these results may have led in recent years to an earlier initiation of treatment of ocular hypertension.

Open-angle glaucoma is primarily treated medically. When the target pressure is not reached by medical treatment, or progression of visual field loss is observed, laser treatment and eventually surgery can be conducted.[50] Normal tension glaucoma will be treated the same way as open-angle glaucoma, with the difference that a much lower IOP is aimed at.

Medication

Glaucoma medication is applied topically on the eye one to four times daily. There is only one systemic drug available for chronic lowering op IOP (acetazolamide). Until 1979 mainly cholinomimetics like pilocarpine were used for glaucoma treatment. Beta-adrenergic antagonists (beta-blockers) were introduced in 1979. Beta-blockers were advised as the first choice medical treatment in POAG in most cases up to 2003.[51] Recently there was a transition from conventional drugs to newer classes of drugs.[52-54] In The Netherlands the latter became especially common practice after the costs of these medications were reimbursed by public health insurance.

New generations of drugs have become available since 1995 (topical carbonic anhydrase inhibitors, alpha$_2$-adrenergic-agonists), 1997 (prostaglandin analogues), 1998 (fixed dorzolamide/timolol combination), and 2002 (prostamide, fixed latanoprost/timolol combination). Docosanoids (unoprostone, 1994) are not available in Western Europe and the United States of America. With the introduction of the second edition of the terminology and guidelines for glaucoma in 2003, the advise is to start with the drug that a physician prefers to use as initial IOP lowering therapy.[50] Per group of drugs, the mode of action, contraindications, topical and systemic side effects are described in table 1.

Beta-adrenergic antagonists

Beta-adrenergic antagonists (beta-blockers) reduce IOP through beta-blocking of the ciliary body which leads to a reduced inflow of aqueous humour in the anterior chamber of the eye. Most beta-blockers are antagonists of both (beta)$_1$ and (beta)$_2$ receptors. For glaucoma treatment there is one selective (beta)$_1$-adrenergic-antagonist. Representatives of beta-blockers are timolol (non selective) and betaxolol (beta$_1$ selective), which lower IOP by approximately 20% to 30% and 15% to 20% respectively (table 1).[3]

Alpha$_2$-adrenergic agonists

Examples of (alpha)$_2$-adrenergic agonists are apraclonidine 1% which is used to prevent peaks in IOP after laser treatment in the anterior eye segment, and apraclonidine 0.5% which is used for at most three months to postpone surgical treatment. The more selective (alpha)$_2$-adrenergic agonist brimonidine can be used for chronic treatment, it lowers IOP by approximately 20 to 30% (table 1).[3]

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors decrease bicarbonate production and therefore the flow of bicarbonate, sodium and water into the posterior camber. In order to decrease the IOP, more than 98 percent of carbonic anhydrase activity must be inhibited. Examples of topical carbonic anhydrase inhibitors are brinzolamide and dorzolamide, both reduce IOP by 15% to 20% (table 1).[3] Dorzolamide is also available as a fixed combination with 0.5% timolol.

Prostaglandins, prostamids and decosanoids

Prostaglandin analogs, prostamids and docosanoids, all increase uveoscleral outflow through the ciliary body, probably by degradation of the extra cellular matrix. The medications in this class are latanoprost and travoprost (prostaglandins), bimatoprost (prostamide), and unoprostone (decosanoids) (table 1). All are applied topically once daily, except decosanoids which are applied twice daily. Average IOP reductions for monotherapy are 25% to 32% for prostaglandins[3], for prostamids 27% to 32%[3], and for decosanoids 13% to 18% (table 1).[3] Latanoprost is also available as a fixed combination with 0.5% timolol.

Miscellaneous

Other types of medication are the oral carbonic anhydrase inhibitors, parasympathomimemic agents and hyperosmotic agents. Since the introduction of the newer classes of glaucoma drugs these have rarely been used for chronic glaucoma treatment.

Laser treatment

In case of insufficient lowering of IOP in POAG, laser treatment (laser trabeculoplasty) is often performed. Most often Argon laser is used to make small effects in the trabecular meshwork. The thermal energy produced by pigment absorption of laser light causes shrinkage of collagen in the trabeculae.[56] With subsequent opening of the trabeculae and decreasing resistance against aqueous humour. To reach a sufficient lowering of the IOP, an open anterior chamber angle and sufficient pigment in the trabeculum is required. Laser trabeculoplasty is painless and can be conducted on out patient basis. The IOP lowering effect is temporary, after 5 years 50% of the patients have inadequately controlled IOP again.[56-59] The treatment can be repeated although the effect is less prominent.

Surgery

Filtration surgery is the standard procedure when medical and laser treatment have failed or progression of visual field loss occurs.[50] Indications for surgery depend on: severity of glaucoma, IOP level, cause of glaucoma, and in some cases age. Trabeculectomy is the standard technique for filtration surgery. The basic principle of this operation is to create an opening in the trabecular meshwork to establish direct communication between the anterior chamber and the subconjunctival space. Nowadays it is possible to combine trabeculectomy with cataract extraction and intraocular lens implant (phacotrabeculectomy). The success of trabeculectomy depends on the number of risk factors for failure in the patient. These are defined as:[60]

Table 1. Description of mode of action, contraindications, and main topical and systemic side effects of groups of glaucoma drugs[3, 50, 55]

Group	Generic product	Mode of action	Contraindications	Topical side effects	Systemic side effects
Non selective beta-blockers	timolol befunolol levobunolol metipranolol	Decrease of aqueous humour production	Asthma, history of obstructive pulmonary disease, sinus bradycardia, heart block	Allergy, irritation, blurring, corneal anaesthesia, keratitis, allergy	Bradycardia, heart block, bronchospasm, decreased libido, central nervous system depression
Selective beta-blockers	betaxolol	Decrease of aqueous humour production	Sinus bradycardia, heart block or cardiac failure, asthma (relative contraindication), history of obstructive pulmonary disease	Blurring, irritation, corneal anaesthesia, punctate keratitis, allergy	Bradycardia, heart block, bronchospasm, decreased libido, central nervous system depression
$Alpha_2$ –selective adrenergic agonists	brimonidine iopidine	Decrease of aqueous humour production Increases aqueous humour outflow	Paediatric age, monoamine oxidase inhibitor usage, anti depressive medication usage, narrow anterior chamber angle and aphakia.	Irritation, allergy, blurring, foreign body sensation, eyelid oedema, dryness	Headache, fatigue, dizziness, bradycardia, tachycardia depression
Prostaglandin derivatives Prostamide Docosanoids	latanoprost travoprost bimatoprost unoprostone	Increases uveoscleral outflow of aqueous humour		Increased iris and lash pigmentation, hypertrichiasis, conjunctival hyperemia, blepharitis, eye pain	Flu like symptoms, joint/muscle pain, headache, increased blood pressure
Topical carbonic anhydrase inhibitors	dorzolamide brinzolamide	Decrease of aqueous humor production	Severe renal disease	Irritation, induced myopia, blurring, keratitis, stinging, burning, conjunctivitis, dermatitis	Headache, nausea, fatigue, bitter taste

- Age less than 40 years old
- African descent
- Diabetes mellitus
- Longstanding medical treatment with miotics or sympathomimetics
- Previous argon laser trabeculoplasty
- Previous ocular surgery (cataract surgery, failed filtration procedure)
- High-risk glaucoma (angle recession glaucoma, uveitic glaucoma and neovascular glaucoma)

The success rate depends on the number of risk factors for failure. In patients at relatively low risk for failure, the one-year success rates are 80- 83%,[60-62] and the 5-year success rates are 54-67%.[61-63]

One of the major problems in trabeculectomy is fibrosis of the conjunctiva which causes increased aqueous resistance and a rise in IOP. To stop this process per- and/or postoperatively fibrosis inhibitors can be applied (mitomycin-C and 5-Fluoruracil).[60, 64] The use of these agents is especially advisable when operating on patients with risk factors for failure.[64-66]

Outline of the thesis

In this thesis the efficacy of new glaucoma drugs is studied, as well as the broader effect of their introduction on the process and outcome of glaucoma treatment. These effects are of interest to ophthalmologists and decision makers because there is an ongoing debate about the optimal place of these new drugs in the practice of glaucoma treatment. Furthermore, the evidence of practice based studies can be used to balance claims that are often based on efficacy studies alone.

The efficacy of glaucoma drugs has been the subject of a multitude of clinical trials with varying results giving rise to the potential for preferred citation. Therefore, a systematic review and meta-analysis on the IOP lowering effects of all currently used glaucoma medication has been carried out. This meta-analysis is presented in chapter 2 and gives an overview of the average intraocular pressure lowering effects of glaucoma monotherapy observed in randomized clinical trials. In a further step a formal statistical test, network meta-analysis, was performed to study the IOP reducing effect between drugs, compare it to timolol and rank the drugs according to their IOP reducing effect (chapter 3). New drugs might not only be used as monotherapy, but also in addition to existing medical therapy. This might be indicated when a substantial IOP reduction is reached with monotherapy, but target pressure is still not achieved.[3, 50] Hence, the IOP reducing effects of latanoprost or dorzolamide added to timolol have been calculated by meta-analysis. This is presented in chapter 4.

While efficacy of drugs can be shown in the experimental conditions of a clinical trial, there is always uncertainty about their effect in everyday practice. To study the latter, and to identify predictors of IOP lowering, data from a large cohort of medically treated glaucoma patients (DURING study) are used (chapter 5).

Drug effects cannot only be compared in individual patients, but their effects can also be evaluated on population level, to detect the clinical value of (new) glaucoma drugs. Chapter 6 describes changes in process and outcome of medical glaucoma treatment from 1995 to 2002 in patients that newly started medical glaucoma therapy. For this purpose process and outcome were compared between the period before (1995-1998) and after (1999-2002) the introduction of new glaucoma drugs. Ultimately, patients who do not achieve sufficient IOP reduction are considered for surgery. In chapter 7, the impact of introduction of new drugs and a treatment protocol for glaucoma on the number of glaucoma surgeries is studied. Finally, in chapter 8, the findings described in this thesis are discussed.

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2

Intraocular pressure-lowering effects of all commonly used glaucoma drugs - a meta-analysis of randomized clinical trials -

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Abstract

Objective: To estimate the intraocular pressure (IOP) reduction achieved by the most frequently prescribed glaucoma drugs and placebo in a meta-analysis of randomized clinical trials.

Design: Meta-analysis of randomized clinical trials

Participants: Twenty-seven articles reporting on 28 randomized clinical trials, these articles reported of 6953 participants for the trough and 6841 for the peak.

Methods: Articles published up to December 2003 were identified in the following data sources: Medline, Embase, and the Cochrane Controlled Trials Register, and references from relevant articles. Over 85% of the patients had to be diagnosed as primary open-angle glaucoma (POAG) or ocular hypertension (OH), articles had to be written in English, German, French, or Dutch. Quality of trials was assessed by a Delphi list with additions. The pooled 1-month IOP-lowering effect from baseline at peak and trough was calculated by performing meta-analysis using the random effects model.

Main Outcome Measures: Absolute and relative change in intraocular pressure from baseline, for peak and trough moments.

Results: Relative IOP reductions from baseline (mean (95% confidence interval) were for 0.5% betaxolol peak -23% (-25;-22), trough -20% (-23;-17), for 0.5% timolol peak -27% (-29;-25), trough -26% (-28;-25), for 2.0% dorzolamide peak -22% (-24;-20), trough -17% (-19;-15), for 1.0% brinzolamide peak -17% (-19;-15), trough -17% (-19;-15), for 0.2% brimonidine peak –25% (-28;-22), trough -18% (-21;-14), for 0.005% latanoprost peak -31% (-33;-29), trough -28% (-30;-26), for 0.004% travoprost peak -31% (-32;-29), trough -29% (-32;-25), for 0.03% bimatoprost peak -33% (-35;-31), trough -28% (-29;-27) and for placebo peak -5% (-9;-1), trough -5% (-10;-0). The difference in absolute IOP reduction from baseline between timolol and prostaglandin analogues or prostamide varied from -0.4 to 0.1 mmHg at trough and from 1.0 to 1.5 mmHg at peak. Quality scores of included studies were generally high, mean 14.2, on a scale from 0 to 20 (interquartile range 13-16).

Conclusion: This meta-analysis suggests that bimatoprost, travoprost, latanoprost and timolol are the most effective intraocular pressure-reducing agents in POAG and OH patients.

Introduction

Glaucoma is the third largest cause of worldwide blindness. It is estimated that, in 2000, 67 million people worldwide had primary glaucoma, with 6.7 million suffering from bilateral blindness.[1] In Caucasians approximately 70% of the glaucoma patients have primary open-angle glaucoma (POAG). The treatment of glaucoma focuses mainly on the reduction of the intraocular pressure (IOP), by drugs, laser or surgery.

In the last decade, several new drugs to lower IOP were introduced. Because these drugs have mechanisms of action and contraindications that are different from the more classical drugs (beta-blockers), the number of treatment options has increased substantially. However, there is controversy as to the degree of reduction of IOP that can be achieved with different drugs. This controversy is fuelled by the preferred citation of studies with a favorable result for certain new drugs and the absence of a recent and adequate systematic review that summarizes the results of the individual clinical trials.

In contrast to the statement that "meta-analysis is not available for any of the drugs used for glaucoma treatment with the exception of beta-blockers"[2], we found two recently published meta-analyses.[3, 4] These two meta-analyses reported on latanoprost versus timolol and latanoprost or brimonidine versus timolol or betaxolol. In these meta-analyses the mean of morning, noon and evening IOPs was calculated, but the calculated summary statistics did not give insight in possible differences between peak and trough effects. This latter issue could be important in clinical practice, because some of the new medications are administrated only once daily. Thus, the differences in effect on IOP between the new drugs and beta-blockers could diverge at peak and trough. Finally, several new studies were published since these two meta-analyses.

Hence, we conducted a meta-analysis of all frequently prescribed drugs for glaucoma, including the prostamide bimatoprost and the prostaglandin analogue travoprost. To improve homogeneity we used strict eligibility criteria. Moreover, we estimated the peak and though IOP reductions of every drug separately.

Methods

Articles were identified trough a computerized search in Medline, Embase, and the Cochrane Controlled Trials Register. The search strategy as advised by the Cochrane Collaboration was used to identify randomized clinical trials.[5-7] The keywords for medication were betaxolol, timolol, dorzolamide, brinzolamide, brimonidine, latanoprost, travoprost and bimatoprost and their commercial names. The keywords for the disease were ocul* and hypert*, explode "Ocular-hypertension"/ all subheadings, glaucom*, explode "Glaucoma"/ all subheadings. Relevant publications were examined for references until no further studies were found.

Potentially eligible for inclusion in our meta-analysis were randomized clinical trials on IOP-lowering drugs, written in English, French, German or Dutch and published up to December 2003. After completion of the searches, title, abstract and Medical Subject Heading (MeSH) words of the obtained publications were used for a rough judgment of an article's eligibility. This was done by one researcher (JSAGS). Of the remaining identified publications, the complete papers were printed or photocopied to judge whether they reported randomized clinical trials. The remaining potentially eligible trials were distributed to either of two researchers (CABW and RvdV), using a computerized list of random numbers. The observers were blinded to the names of the authors and their institutions, the names of the journals, sources of funding and acknowledgements as well as the financier of the study.[6, 8]

Trials were excluded if they did not include one of the medications listed in table 1 or a placebo in 2 or more of their study arms. Other exclusion criteria are listed in figure 1.

Table 1. Drugs included in the meta-analysis with the most commonly prescribed regimen and moment chosen for peak and trough measurement

Drug	Concentration (%)	Dosing frequency	Moment of administration	Peak	Trough
timolol	0.5	twice daily	morning, evening	2h after morning administration	12h after evening administration
betaxolol	0.5	twice daily	morning, evening	2h after morning administration	12h after evening administration
brimonidine	0.2	twice daily	morning, evening	2h after morning administration	12h after evening administration
dorzolamide	2.0	twice or 3 times daily	morning, (afternoon), evening	2h after morning administration	12h after evening administration
brinzolamide	1.0	3 times daily	morning, afternoon, evening	2h after morning administration	12h after evening administration
latanoprost	0.005	once daily	evening	12h after evening administration	24h after evening administration
travoprost	0.004	once daily	evening	12h after evening administration	24h after evening administration
bimatoprost	0.03	once daily	evening	12h after evening administration	24h after evening administration

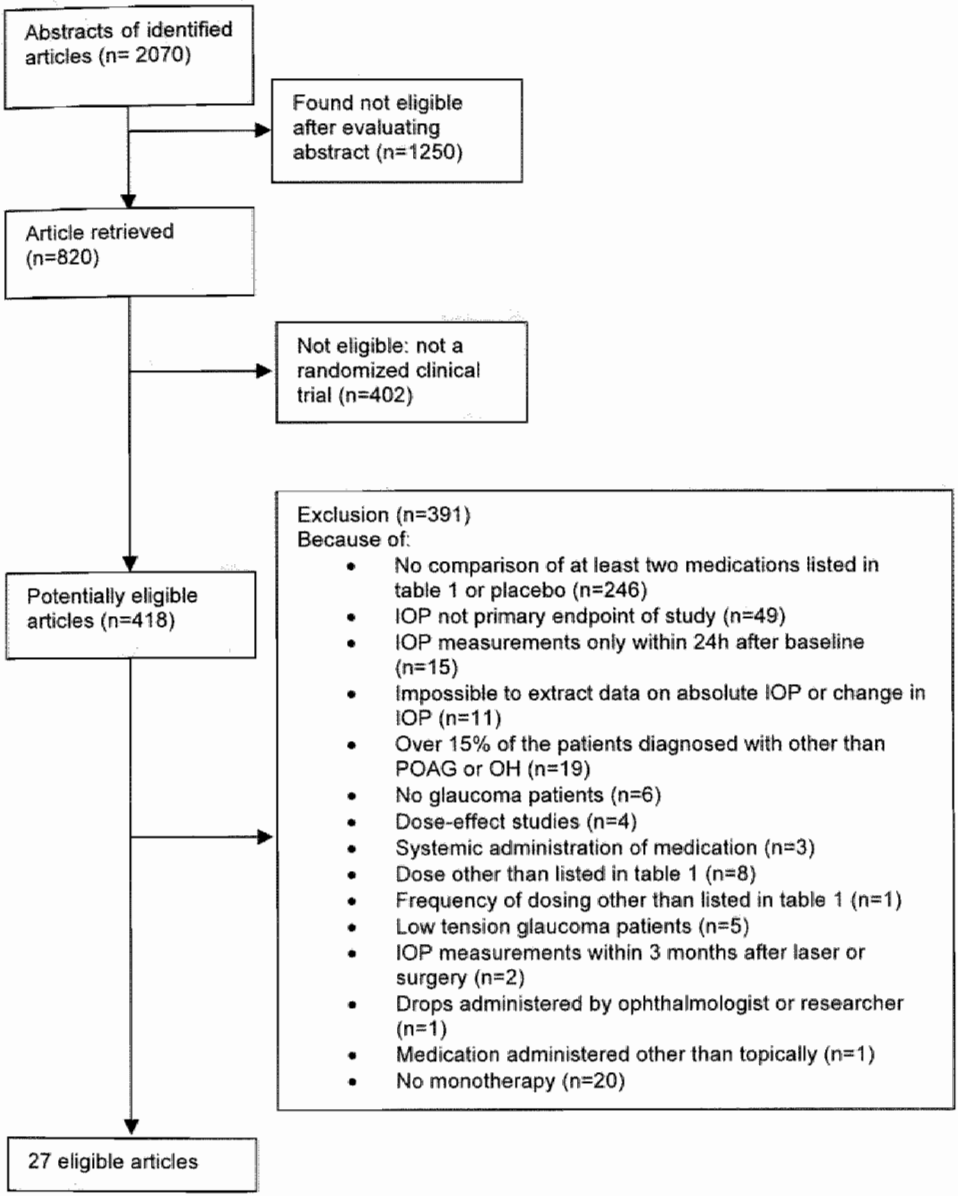

Figure 1. Flowchart of selection of studies. IOP = intraocular pressure; OH = ocular hypertension; POAG = primary open-angle glaucoma

The reason for exclusion was recorded on a standard form. In case more than one reason for exclusion was present, only the first reason encountered was listed in figure 1. Excluded publications were reassessed to make sure all eligible publications were included. At the start of this selection process, there were common meetings with a third researcher (JSAGS). After this, 25 articles were judged by 2 researchers independently to evaluate agreement in judgment of inclusion or noninclusion, and yielded a kappa of 1.0.

Data from included articles were extracted using a standard form. Operationalization of the items on this form was achieved by consensus meetings of the 3 researchers (JSAGS, CABW, RvdV), before the process of data abstraction began. The 3 researchers met on a regular basis to discuss any ambiguity.

Quality assessment

Methodological quality was evaluated using the Delphi list[9] with additional items. Items specifically important for interpreting IOP measurements were also added (table 2). Each item in this quality list had the same weight. For each publication, a quality score was calculated, where "yes" was scored as 1 point for a certain quality item and "no" and "do not know" were scored as 0 points. For scoring quality items on masking, allocation concealment and intention-to-treat analysis, we used suggestions from Berger et al.[10-13]

Outcome measure

The outcome measure was the change in IOP at 1 month from baseline. In case the measurement at 1 month was not present, the first measurement after 1 month was accepted with a maximum of 6 months. In absence of an IOP value reported in a table or text, the IOP was measured when presented in a figure. If no IOP at 1 month from baseline was reported in a figure, the value was measured at another point in time, using the earlier mentioned sequence. In case of a crossover design, only data were extracted from the period before crossing over of therapies. Figures used to extract data were electronically scanned and viewed at full screen size (1400 x 1050 pixels). A digital ruler was used to measure the number of pixels corresponding with the IOP baseline value and the value corresponding with change in IOP was measured. All figures were read by the same researcher (CABW).

Original data were obtained from the articles as much as possible, data that could not be obtained were to be calculated when necessary. When the number of patients at a relevant point in time was not reported, this respective number was calculated using the number of patients lost to follow-up. In case the moment of loss to follow-up was unclear, overall number of patients lost to follow-up was used to calculate the number of patients at the relevant time point. In case no data on the number of patients lost to follow-up were present, the number of patients at baseline was used as an estimate.

Peak and trough measurements were noted (table 1). Peak and trough moments for each medication were as advised by the American Academy of Ophthalmology.[14] In case dorzolamide monotherapy was administrated three times daily, morning measurements were included in the analysis.

Table 2. Quality items included for quality assessment, source from which the quality item was obtained, number of publications that scored a positive quality score, per quality item

Item code	Source[9]	Quality item	Number of publications scored "yes"
A	Delphi list	Was a method of randomization performed?	27
B	Added by authors*	Is the period of outcome measurements equal for all groups?	27
C	Considered for Delphi list	Is it unlikely that compliance may explain differences between groups?	27
D	Added by authors	Are side effects reported?	26
E	Added by authors	Was a short and a long term follow-up IOP measurement performed?	26
F	Added by authors	Is the time of IOP measurements equal for all groups?	26
G	Delphi list†	Were inclusion criteria specified?	25
H	Delphi list†	Were exclusion criteria specified?	25
I	Considered for Delphi list	Are the interventions described explicitly?	25
J	Delphi list	Were the groups similar at baseline regarding the most important prognostic indicators?	22
K	Delphi list	Were point estimates and measures of variability presented for the primary outcome measures?	21
L	Added by authors	Is information about the method of IOP measurement presented?	20
M	Added by authors	Is the time between applying the eye drop and IOP measurement equal for all groups?	20
N	Considered for Delphi list	Was co-medication avoided or standardized?	19
O	Delphi list	Was the patient masked to the treatment?	16
P	Considered for Delphi list	Was calculation of statistical power reported after allocation to the treatment?	16
Q	Delphi list	Was an intention-to-treat analysis performed?	15
R	Delphi list	Was the treatment allocation concealed?	0
S	Delphi list	Was the outcome assessor blinded?	0
T	Delphi list	Was the care provider blinded?	0

*the authors added items specifically important for interpreting IOP measurements, † item split into inclusion and exclusion criteria

Three publications did not report peak or trough moments, just means of measurements over the day. These means were used in the calculation of peak as well as trough values.[15-17] If a study appeared in more than one publication, the most recent results with complementary data from previous papers were used for statistical analysis. In one article results from earlier studies were

combined with new data. However, in this publication trough values were not presented.[18] Therefore these values were extracted from two earlier studies.[19, 20]

Statistical analysis

Absent absolute values were calculated by use of the baseline value and the difference from baseline. In case standard deviation (SD) could not be obtained from the publication, it was calculated using the number of patients and standard error of the mean (SEM). In case neither an SD nor an SEM of the follow-up measurement was available, baseline SD was used as an estimate of the SD of the follow-up measurement.

In 2 publications only the *P* value for the difference in IOP values between arms was reported as a measure of deviation.[21, 22] The *P* value and the sample sizes of the arms were used to calculate the SD of the difference in IOP between baseline and follow-up measurement.

In absence of a reported difference in IOP between baseline and follow-up measurement, change in IOP was calculated. In absence of a SD of the change in IOP this SD was calculated by the formula:

$$\mathrm{Var}(\mathrm{IOP}_{f\text{-}u} - \mathrm{IOP}_{bl}) = \mathrm{Var}(\mathrm{IOP}_{f-u}) + \mathrm{Var}(\mathrm{IOP}_{bl}) - 2\rho\,\mathrm{SD}(\mathrm{IOP}_{bl})\,\mathrm{SD}(\mathrm{IOP}_{f-u})$$

$$\rho = \frac{\mathrm{Var}(\mathrm{IOP}_{f\text{-}u}) + \mathrm{Var}(\mathrm{IOP}_{bl}) - \mathrm{Var}(\mathrm{IOP}_{f\text{-}u} - \mathrm{IOP}_{bl})}{2\,\mathrm{SD}(\mathrm{IOP}_{bl})\,\mathrm{SD}(\mathrm{IOP}_{f\text{-}u})}$$

$$\text{Where } \mathrm{SD}(\mathrm{IOP}_{f\text{-}u} - \mathrm{IOP}_{bl}) = \sqrt{\mathrm{Var}(\mathrm{IOP}_{f\text{-}u} - \mathrm{IOP}_{bl})}$$

$$bl = \text{baseline}, \quad f-u = \text{follow}-\text{up}$$

The correlation coefficient ρ indicates correlation between baseline SD and SD of the follow-up measurement, as calculated out of the results of all studies reporting complete data on: IOP baseline measurement and SD, follow-up measurement and SD, difference between baseline and follow up measurement and SD.[15, 23-26] The value of this correlation coefficient is 0.5. In case no relative reduction was reported, this was calculated from of the absolute change in IOP. The SD of relative change (%) was calculated as:

$$\mathrm{SD}_{\text{relative change}} = \frac{\mathrm{SD}_{\text{change}}}{\mathrm{IOP}_{\text{baseline}}}$$

Pooled IOP values were calculated using a random effects model with STATA.[27]

To detect publication biases, we explored asymmetry in funnel plots. These were examined visually; furthermore Egger's measure of publication bias was calculated.[28]

Results

Study eligibility and quality

The flow of the randomized clinical trials included in our analysis is shown in figure 1. The characteristics of the eligible studies are summarized in table 3. In general, the quality of included studies was high (table 3). The mean total quality score for all studies is 14.2, on a scale from 0 to 20 (interquartile range 13 to 16). Twenty-six articles were included that reported on 27 trials, 56 arms were reporting peak measurements, and 52 arms trough measurements. We included 6953 subjects for peak and 6861 for trough. We could not identify heterogeneity in funnel plots. *P* values for absolute change from baseline Egger's measure for publication bias were 0.57 at peak and 0.36 at trough. For relative change from baseline these *P* values were 0.36 at peak and 0.22 at trough. Therefore, no publication bias was found. Because neither by eye-balling, nor by statistics relevant differences in measures for publication bias were observed, only a single funnel plot is presented (figure 2).

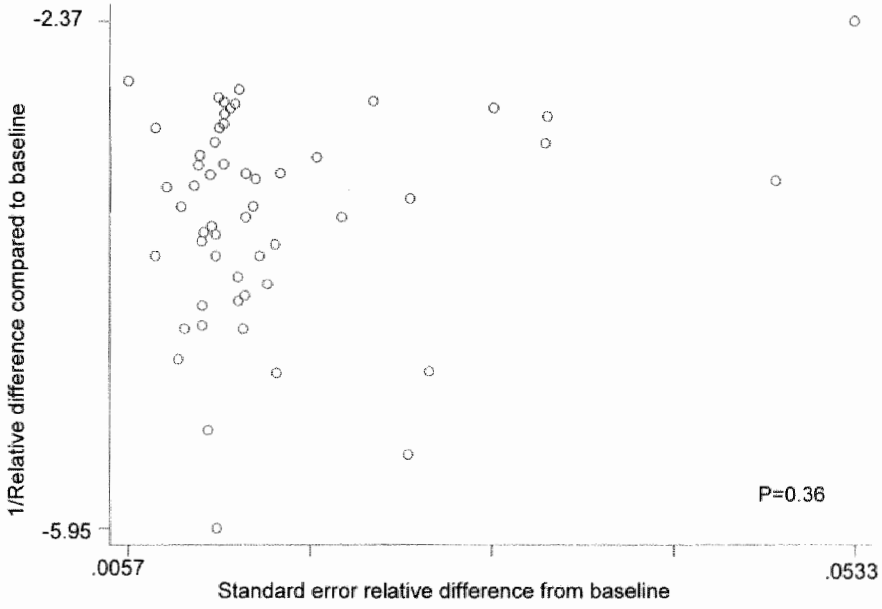

Figure 2. Funnel plot, relative change from baseline at peak moment and *P* value of Egger's measure for publication bias

Table 3. Baseline characteristics included publications

Trial	Medication	Country	Endpoint measurement	Number of patients at baseline
Rusk et al., 1998[35]	betax vs dorzo	USA	1 month	311
Strahlman et al., 1995[26]	betax vs dorzo vs tim	USA	1 month	568
Nordmann et al., 2002[36]	betax vs tim	France	3 months	278
Stewart et al., 1986[16]	betax vs tim	USA	1 month§	29
Collignon Brach et al., 1992[37]	betax vs tim	Belgium	3 months	20
Noecker et al., 2003(1)[21]	bimato vs latano	USA	1 month‖	269
Gandolfi et al., 2001[38]	bimato vs latano	Italy	3 months	232
Dubiner et al., 2001[24]	bimato vs latano vs plac	USA	1 month	64
Parrish, et al. 2003[23]	bimato vs latano vs travo	USA	3 months	410
Brandt et al., 2001[19]	bimato vs tim	USA	3 months‖	353
Whitcup et al., 2003[20]	bimato vs tim	USA	3 months‖	362
Higginbotham et al., 2002[18]	bimato vs tim	Australia	6 weeks	715
Noecker et al., 2003(2)[48]	bimato vs travo	USA	1 month	31
Kampik et al., 2002[15]	brimo vs latano	Germany	6 months§	379
DuBiner et al., 2001[39]	brimo vs latano	USA	1 month	127
Schuman, 1996[40]	brimo vs tim	USA	1 month	926**
Sall, et al 2000[29]	brinzo vs dorzo vs plac	USA	1 month	294
O'Donoghue et al., 2000[41]	dorzo vs latano	UK	3 months	224
Wilkerson et al., 1993[35]	dorzo vs placebo	USA	1 month	48
Boyle et al., 1998[25]	dorzo vs tim	USA	1 month	221
Alm et al., 1995[42]	latano vs tim	Scandinavia	3 months	178
Camras et al., 1996[43]	latano vs tim	USA	6 months‖	268
Aquino and Lat-Luna, 1999[17]	latano vs tim	Philippines	6 weeks§	60
Watson et al., 1996[44]	latano vs tim	UK	6 months (peak) 6 weeks (trough)	294
Netland et al., 2001[22]	latano vs tim vs travo	USA	6 weeks	585
Fellman et al., 2001[45]	tim vs travo	USA	6 weeks	396
Goldberg et al., 2001[46]	tim vs travo	USA	6 weeks (8am and 10 am), 3 months (4pm)	382

Betax = betaxolol, bimato= bimatoprost, brimo = brimonidine, brinzo = brinzolamide, dorzo= dorzolamide,
*Pooled value, measurements closest to 8am, †Open-angle glaucoma or ocular hypertension, ‡Open-angle glaucoma, chronic angle-closure glaucoma with patent iridectomy, pseudoexfoliative glaucoma or pigmentary glaucoma,
††Primary open-angle glaucoma or ocular hypertension,
nr = not reported, POAG = primary open-angle glaucoma, OH = ocular hypertension, SD = standard deviation

Intraocular pressure lowering

In table 4, absolute and relative change from baseline and a 95% confidence interval are presented. The pooled change from baseline for placebo was –1.3 mmHg at trough and –1.6 mmHg at peak. Trough change from baseline achieved by glaucoma monotherapy varied from van –4.5 mmHg for brimonidine, to –7.0 mmHg for travoprost. Change from baseline at peak varied from –4.4 mmHg for brinzolamide to –8.4 mmHg for bimatoprost.

Table 3. Continued

Withdrawals (%)	Sex (male /female)	Mean age (years)	Types of glaucoma			Baseline IOP mmHg (mean (SD))*	Quality score	Quality criteria not fulfilled
			POAG	OH	Others			
5.1	138/173	64	nr†	nr†	nr†	24.8 (4.7)	14	l, n, o, r, s, t
9.9	243/280	62	371‡	197	nr‡	26.8 (4.9)	17	r, s, t
5.0	150/128	63	135	128	15	24.4 (2.7)	16	o, r, s, t
0.0	12/17	65	11	18	0	28.3 (2.9)	14	n, p, q, r, s, t
nr	nr	60	20	0	0	24.3 (3.8)	5	d, f, g, h, i, j, l, m, n, o, p, q, r, s, t
7.4	103/166	61	155	93	21	24.9 (2.7)	18	r, s, t
7.8	87/145	62	138	81	13	25.7 (3.8)	16	o, r, s, t
7.8	29/35	66	29	35	0	25.5 (2.6)	15	o, q, r, s, t
6.8	172/238	65	309	95	6	25.6 (2.9)	16	o, r, s, t
5.1	145/208	63	227¶	126	nr¶	26.0 (3.3)	18	r, s, t
5.0	162/200	60	186¶	176	nr¶	25.9 (3.1)	15	k, m, o, r, s, t
16.0	307/408	62	413¶	302	nr¶	25.9 (3.1)	14	k, l, n, r, s, t
6.5	11/20	65	28	3	0	26.0 (1.6)	13	k, l, p, q, r, s, t
12.6	154/225	65	284	64	31	22.8 (3.0)	13	j, m, o, p, r, s, t
5.5	52/75	61	93	34	0	24.3 (2.1)	15	p, q, r, s, t
9.6	421/416	62	513	324	0	24.8 (3.2)	13	l, o, p, q, r, s, t
6.8	131/163	64	217	70	7	26.5 (2.4)	16	q, r, s, t
4.9	130/94	67	120	88	16	27.7 (3.6)	12	m, n, o, p, q, r, s, t
8.3	23/25	63	nr††	nr††	0	27.1 (3.7)	11	e, j, n, o, p, q, r, s, t
2.2	117/104	62	nr†	nr†	nr†	28.0 (4.6)	17	l, r, s, t
nr	43% male	66	nr‡‡	nr‡‡	nr‡‡	24.5 (3.2)	8	g, h, i, j, l, m, n, p, q, r, s, t
7.5	152/154	62	84	170	14	25.3 (4.1)	17	p, r, s, t
5.0	38/22	57	55	4	1	29.3 (9.1)	13	j, o, p, q, r, s, t
8.8	191/103	65	121	148	25	26.3 (3.8)	17	q, r, s, t
1.9	296/289	nr	396	181	8	26.9 (3.8)	17	k, r, s, t
2.7	188/208	64	251	132	13	27.3 (5.4)	16	k, m, r, s, t
nr	192/190	63	208	147	27	27.3 (2.9)	16	k, m, r, s, t

latano = latanoprost, tim = timolol, travo = travoprost, plac = placebo
§mean of peak and trough, ||Data measured out of figures, ¶Chronic open-angle glaucoma,
**2 studies reported in the same publication, demographics only presented for per protocol analysis (n=837),
‡‡Primary open-angle glaucoma, ocular hypertension, capsular glaucoma or pigmentary glaucoma

Calculated in relative measures, placebo gave a 5% change from baseline at trough as well as at peak. Relative change from baseline at trough ranged from –17% for brinzolamide and dorzolamide, to –29% for travoprost. At peak, changes for baseline vary from –17% for brinzolamide to -33% for bimatoprost (table 4). The results did not substantially differ when studies reporting 6-month results or 6-month and 3-month results were left out in the analysis. For brinzolamide, only one eligible publication was found, therefore the effects as reported in the publication are reported in table 4.[29]

Table 4. Absolute and relative change in intraocular pressure from baseline, number of studies

Group	Generic product	Absolute change (mmHg)		Relative change (%)		Number of Studies	References
		Mean difference from baseline	95% Confidence limits	Mean difference from baseline	95% Confidence limits		
Placebo	placebo, trough	-1.3	-2.4; -0.3	-5	-9; -1	3	24, 29, 35
	placebo, peak	-1.6	-2.7; -0.5	-5	-10; 0	3	24, 29, 35
Beta-blockers	betaxolol, trough	-5.2	-6.3; -4.1	-20	-23; -17	4	16, 26, 36, 47
	betaxolol, peak	-6.0	-6.6; -5.3	-23	-25; -22	5	16, 26, 35, 37, 47
	timolol, trough	-6.9	-7.4; -6.5	-26	-28; -25	15	16, 17, 19, 20, 22, 25, 26, 36, 40, 42-46
	timolol, peak	-6.9	-7.5; -6.3	-27	-29; -25	15	16-18, 22, 25, 26, 36, 37, 40, 42-46
Prostaglandin analogues Prostamide	bimatoprost, trough	-6.5	-6.8; -6.1	-28	-29; -27	6	19-21, 23, 24, 38
	bimatoprost, peak	-8.4	-9.0; -7.8	-33	-35; -31	6	18, 21, 23, 24, 38, 48
	latanoprost, trough	-6.8	-7.6; -6.1	-28	-30; -26	11	15, 17, 18, 21-24, 38, 41-44
	latanoprost, peak	-7.9	-8.3; -7.4	-31	-33; -29	12	15, 17, 18, 21-24, 38, 39, 41-44
	travoprost, trough	-7.0	-8.2; -5.7	-29	-32; -25	4	22, 23, 45, 46
	travoprost, peak	-8.2	-8.7; -7.7	-31	-32; -29	5	22, 23, 45, 46, 48
Alpha$_2$-adrenergic agents	brimonidine, trough	-4.5	-5.2; -3.8	-18	-21; -14	3	15, 40
	brimonidine, peak	-6.1	-6.7; -5.4	-25	-28; -22	4	15, 39, 40
Carbonic anhydrase inhibitors	brinzolamide, trough	-4.5	-5.1; -3.9	-17	-19; -15	1	29
	brinzolamide, peak	-4.4	-5.0; -3.8	-17	-19; -15	1	29
	dorzolamide, trough	-4.5	-5.0; -4.0	-17	-19; -15	6	25, 26, 29, 35, 41, 47
	dorzolamide, peak	-5.9	-6.5; -5.2	-22	-24; -20	6	25, 26, 29, 35, 41, 47

Discussion

Our results confirm that the 8 drugs evaluated in this meta-analysis lower IOP more effectively than placebo. The highest reduction in IOP at peak was achieved by bimatoprost (33%), followed by latanoprost, travoprost, timolol, brimonidine, betaxolol, dorzolamide, brinzolamide (17%) and placebo (5%). At trough this order is travoprost (31%), bimatoprost, latanoprost, timolol, betaxolol, brimonidine, brinzolamide, dorzolamide (17%) and placebo (5%). However, the differences between prostaglandin analogues, prostamide and timolol are small, especially at trough. We believe that our results are robust since the quality of the included studies was generally high, with a mean quality score of 14.2 on a scale 0 to 20.

Several methodological aspects of our meta-analysis deserve further consideration. We selected trials in which the concentration of drug, the moment of applying and frequency of dosing were as recommended by the American Academy of Ophthalmology.[14] This implies that the IOP reductions observed in this meta-analysis can be achieved in daily practice. Furthermore, the separate analysis of IOP reduction at peak as well as trough enables a more accurate comparison of the merits of the individual drugs.

The primary indication for the investigated drugs is a diagnosis of POAG or OH; therefore, we aimed to include a homogeneous population with these conditions. However, 8 of the 27 included trials did not specify diagnosis completely, and reported of OAG and OH. These studies were included. A study conducted by the present authors showed that in cohort of pharmaceutically treated glaucoma patients 93% of the OAG and OH patients were diagnosed with POAG or OH (unpublished data). Hence, we are confident that at least 85% of patients in each of the studies included had the condition of interest.

We scored the quality of studies included in our meta-analysis to assess the robustness of our summary estimates of effects. Out of the >60 methods that are available for validity assessment of randomized clinical trials we chose the Delphi list.[9] The Delphi list has been developed after consensus meetings between experts on quality assessment from different fields, which enhances content and face validity. In addition we added some items that are of major importance for the quality assessment of randomized clinical trials studying IOP-lowering effects of glaucoma medication (table 2). In general, in most reports on randomized trials too little or insufficient information is provided to be able to properly judge whether randomization and masking were adequate and whether allocation of treatments was truly concealed.[10-12] Unfortunately, also for quantifying possible baseline imbalances in most cases insufficient data are available.[13] Moreover, authors often mention the process of masking but seldom report whether masking was successful.[13] When studying glaucoma medication true masking is hard since differences in side effects may reveal a patient's treatment. The latter issue, and the issue on reporting success of masking

addressed by Berger et al.[10-12] resulted in an overall score of zero for the items "Was the care-provider blinded?" and "Was the outcome assessor blinded?" A weaker point of the present study is the fact that the first judgment on eligibility of articles based on the title, abstract and MeSH was performed by a single researcher; ideally, 2 independent observers should screen the abstracts.[7] However, the purpose of this first selection was to exclude publications that were obviously ineligible for inclusion (e.g. studies on healthy subjects, animals, excluded drugs, or IOP not as primary outcome). These issues are easy to assess, based on abstract and title or MeSH keywords. Therefore, it is not likely that eligible studies were rejected in this stage of study selection. This is confirmed by the fact that any of the publications used for the two meta-analyses of Zhang and Einarson[3, 4] were present among the possible eligible articles that remained after this first selection. Moreover, if any doubt on eligibility of a study was present after reading the title, abstract and MeSHs, the complete publication was copied, and included in the further selection process.

Also potentially eligible trials were randomly assigned to a single researcher for final judgment on the eligibility of these trials. However, eligibility criteria were extensively discussed to make the level of agreement between both reviewers as high as possible. In addition, if any doubt about the eligibility of a publication rose, this was discussed with the other 2 researchers.

Potentially eligible publications were divided randomly between 2 researchers to prevent bias. To minimize information bias[30], the observers were blinded to the names of the authors and their institutions, the names of the journals, sources of funding and acknowledgements.[31] We minimized language bias by including not only English but also studies published in German, French and Dutch.[32, 33] We aimed to minimize database bias by searching in multiple databases (Medline, Embase, and Cochrane Controlled Trials Register)[34] and by checking references in selected publications. We did not use references from all reviews published to prevent citation bias.[34] We minimized multiple publications bias by checking the studied populations and paying extra attention when including multicenter studies. We found 4 publications reporting on the same study population. The article reporting the final results was used for this meta-analysis[18]; data that could not be obtained from this publication were obtained from 2 publications reporting earlier results.[19, 20]

Two other meta-analyses were published on IOP lowering effects of glaucoma drugs. Zhang et al reported IOP reductions at 3 months from baseline of 30% for latanoprost and of 27% for timolol.[3] These findings are comparable to the results of the present study, we found 31% at peak and 28% at trough for latanoprost and 27% at peak and 26% at trough for timolol. Einarson et al[4] compared peak measurements for brimonidine to a combination of trough, peak and diurnal measurements for latanoprost. The 26% IOP reduction for brimonidine from baseline at 3 months of this measurement was comparable to the 25% reduction at peak found in the present study. The value of 33% reduction from baseline for latanoprost at 3 months was higher than the 28% and 31% reduction at trough and peak respectively, found in the present study and in the study of Zhang et al.[3] In general, one may state that our estimations

for IOP reduction are comparable or slightly lower than those reported in earlier published meta-analyses.[3, 4]

Except from the advantage to discriminate between peak and trough moments, the present study has the advantage that the studies included did not vary in concentration of drug, moment of applying and frequency of dosing for the different medicines, and included more drugs. This contrasts with the trials included in the earlier mentioned meta-analyses.[3, 4] Moreover, the present study also reports on drugs that have not been studied by meta-analysis before.

The results of this study show that prostamide or prostaglandin analogues are most effective for lowering IOP by monotherapy in POAG or OH patients. However, the beta-blocker timolol is almost as effective and, thereby, still a good treatment option. The beta-blocker betaxolol, alpha$_2$-adrenergic agent brimonidine, carbonic anhydrase inhibitors, brinzolamide and dorzolamide are clearly less effective. Whether these results are also applicable to patients with other forms of glaucoma remains uncertain.

Because differences between timolol, prostamide, and prostaglandin analogues in IOP reduction are small, other aspects like patient characteristics, quality of life, compliance and costs may be taken into consideration as suggested by the European Glaucoma Society, to decide on the starting therapy for POAG or OH. Depending on the number of randomized clinical trials on IOP-lowering effects that will be published in coming years, in the future an update of this meta-analysis may be desirable. Drug use under everyday circumstances may differ from the situation in a clinical trial due to the selection of patients and the experimental circumstances.[49] Therefore, apart from more controlled research as performed in clinical trials, also observational research on IOP reduction reached by glaucoma medication is desired. In summary, this meta-analysis of randomized comparisons shows that there are multiple options for effective monotherapy in POAG and OH. This enables physicians to tailor an optimal strategy for an individual patient.

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3

Ranking of glaucoma medication

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Abstract

Objective: To present a rank order in IOP reducing capacity of all commonly glaucoma drugs, by comparing them to timolol.

Design: Network meta-analysis of randomized clinical trials

Participants: 27 articles reporting on 28 randomized clinical trials, these articles reported of 6953 participants for trough moment and 6841 for peak moment.

Methods: Network meta-analysis was used to combine within-trial between-drug comparisons, with indirect comparisons from the other trials. Data from a previous meta-analysis were used.

Results: All drugs statistically significantly differ from placebo in lowering IOP. At peak moment the rank order from high to low in achieved mean IOP reduction is bimatoprost, travoprost and latanoprost, brimonidine, timolol, dorzolamide, betaxolol, brinzolamide. At trough moment this rank order is bimatoprost, latanoprost, travoprost, timolol, betaxolol, dorzolamide, brinzolamide, brimonidine. At peak, bimatoprost, travoprost and latanoprost reduce IOP significantly more than timolol, the absolute difference is 1.7 to 2.2 mmHg. At trough, bimatoprost was the only drug that reduced IOP significantly more than timolol, this absolute difference is 1 mmHg. Timolol reduced IOP more than betaxolol, dorzolamide, and brinzolamide.

Conclusion: Network meta-analysis shows that indirect comparison of these drugs is reliable. There is a rank order in glaucoma medications, but differences compared to timolol seem to be small.

Introduction

Ranking of glaucoma drugs according to their intraocular pressure (IOP) reducing effect is difficult. Empirical research would require a direct comparison of all drugs in one trial. Such a trial never has been, or will be, conducted. However, recently a meta-analysis of all commonly used glaucoma drugs has been published.[1] This meta-analysis gave mean IOP lowering effects, but could not make a formal statistical comparison between the drugs.

A conventional meta-analysis would only consider head to head comparisons of drugs. In this case indirect evidence is ignored and usually for most comparisons few studies are available. For example, no trials have compared betaxolol to prostaglandin analogues, which are indicated in case timolol is contraindicated, but both have been compared to timolol. Recently, network meta-analysis was introduced, a new method to compare the effect of drugs by using a formal statistical test taking direct as well as indirect evidence into account.[2, 3] Hence, it was of interest to use the data from our previous meta-analysis for a network meta-analysis to compare and rank all commonly used glaucoma medication.

Methods

The search strategy and method of data extraction are the same as in our previous systematic review.[1] However we adapted an enhanced method of analysis. For the analysis, the absolute and relative change in IOP from baseline and its standard errors were calculated and combined using network meta-analysis.[3] In this network meta-analysis all available direct and indirect comparisons on IOP lowering effects of glaucoma medications were combined. The details on this technique are described by Lumley.[3]

The reliability of treatment effects was assessed by computing the differences between various comparisons of the same two treatments. The variance of these differences over and above what would be expected from sampling error within each trial is expressed as a variance estimate called "incoherence" of the network meta-analysis. Incoherence is reported on the same scale as the outcome (mmHg and %). When the incoherence is substantially smaller than a clinically meaningful difference and substantially smaller than the standard errors of the estimated effect, combining the trials is appropriate.[3]

In total 36 direct comparisons for peak and 34 for trough were available. Depending on the outcome, the indirect comparisons used information from 1 to 5 trials or pairs of trial arms.

In this study we aimed to test the differences in IOP lowering effects of all commonly used monotherapy strategies in patients diagnosed with primary open-angle glaucoma and ocular hypertension. We compared the drugs with timolol 0.5% twice daily, since it is considered as conventional standard

therapy. A negative difference means an agent reduces IOP more effectively than timolol.

We analyzed direct and indirect estimations separately, no or only small differences were observed (data not shown).

Results

In this network meta-analysis, we combined randomized clinical trial data from 27 articles and 28 trials that included 6841 patients at peak and 6953 patients at trough randomized to 9 monotherapy treatment strategies.

The estimates for incoherence in this network meta-analysis were very small, for the absolute comparisons 0.01 mmHg for peak, and 0.002 mmHg for trough. For the relative comparisons incoherence was 0.0002% for peak and 0.0001% and for trough. Analyzing the data ignoring the possibility of incoherence, gave similar results. Here we present the data taking incoherence into account.

The outcomes show that all drugs statistically significantly differ from placebo in lowering IOP. At peak the rank order in reached mean IOP reduction is bimatoprost, travoprost and latanoprost, brimonidine, timolol, dorzolamide, betaxolol, brinzolamide (table 1). At trough this rank order is bimatoprost, latanoprost, travoprost, timolol, betaxolol, dorzolamide, brinzolamide, brimonidine (table 2). At peak bimatoprost, travoprost and latanoprost reduce IOP statistically significantly more than timolol, by 1.7 to 2 mmHg. At trough bimatoprost was the only drug that reduced IOP statistically significantly more than timolol, by 1 mmHg, and reduction of latanoprost and travoprost did not differ significantly from timolol. Forest plots of the results are presented in figure 1.

Discussion

In this network meta-analysis, we combined randomized clinical trial data from 28 trials that included 6841 patients at peak and 6953 patients at trough randomized to 9 monotherapy treatment strategies.

The outcomes show that all drugs reduce IOP significantly more than placebo, and that at peak bimatoprost, travoprost and latanoprost reduce IOP significantly more than timolol. At trough bimatoprost was the only drug that reduced IOP significantly more than timolol, although travoprost and latanoprost had similar estimated reductions. At trough timolol reduces IOP significantly more than brinzolamide, and at peak and through, more than betaxolol, brimonidine and dorzolamide.

Table 1. Absolute (mmHg) and relative (%) change in peak intraocular pressure reached of the most commonly used glaucoma drugs and placebo compared to timolol, calculated by network meta-analysis*

	Peak, absolute difference with timolol (mmHg)		Peak, relative difference with timolol (%)	
Drug	Difference (95% CI)	*P* value for difference with timolol	Difference (95% CI)	*P* value for difference with timolol
bimatoprost	-2.2 (-2.9 to -1.5)	<0.001	-8 (-11 to –6)	<0.001
travoprost	-1.8 (-2.5 to -1.1)	<0.001	-6 (-9 to –3)	<0.001
latanoprost	-1.7 (-2.3 to -1.2)	<0.001	-6 (-9 to –4)	<0.001
brimonidine	-0.5 (-1.4 to 0.4)	0.30	-1 (-5 to 2)	0.39
dorzolamide	0.9 (0.2 to 1.7)	0.02	4 (2 to 7)	0.002
betaxolol	1.5 (0.8 to 2.2)	<0.001	7 (4 to 9)	<0.001
brinzolamide	1.6 (0.3 to 2.9)	0.01	8 (4 to 13)	0.001
placebo	4.1 (3.2 to 5.0)	<0.001	18 (15 to 22)	<0.001

Abbreviation: CI, confidence interval

* positive numbers mean that timolol reduced intraocular pressure more than the comparison therapy. The incoherence estimates were 0.01mmHg for absolute peak intraocular pressure and 0.0002% for relative peak intraocular pressure.

Table 2. Absolute (mmHg) and relative (%) change in trough intraocular pressure reached of the most commonly used glaucoma drugs and placebo compared to timolol, calculated by network meta-analysis*

	Trough, absolute difference with timolol (mmHg)		Trough, relative difference with timolol (%)	
Drug	Difference (95% CI)	*P* value for difference with timolol	Difference (95% CI)	*P* value for difference with timolol
bimatoprost	-1.0 (-1.5 to -0.4)	<0.001	-6 (-8 to –4)	<0.001
latanoprost	-0.2 (-0.6 to 0.3)	0.51	-3 (-4 to –1)	0.004
travoprost	-0.1 (-0.7 to 0.5)	0.70	-3 (-5 to –1)	0.016
betaxolol	1.4 (0.8 to 1.9)	<0.001	5 (3 to 8)	<0.001
brinzolamide	1.5 (0.7 to 2.4)	<0.001	6 (3 to 9)	<0.001
dorzolamide	1.6 (1.0 to 2.1)	<0.001	6 (3 to 8)	<0.001
brimonidine	2.1 (1.3 to 2.8)	<0.001	7 (4 to 10)	<0.001
placebo	3.9 (3.2 to 4.5)	<0.001	15 (13 to 17)	<0.001

Abbreviation: CI, confidence interval

* positive numbers mean that timolol reduced intraocular pressure more than the comparison therapy. The incoherence estimates were 0.002 mmHg for absolute peak intraocular pressure and 0.0001% for relative peak intraocular pressure.

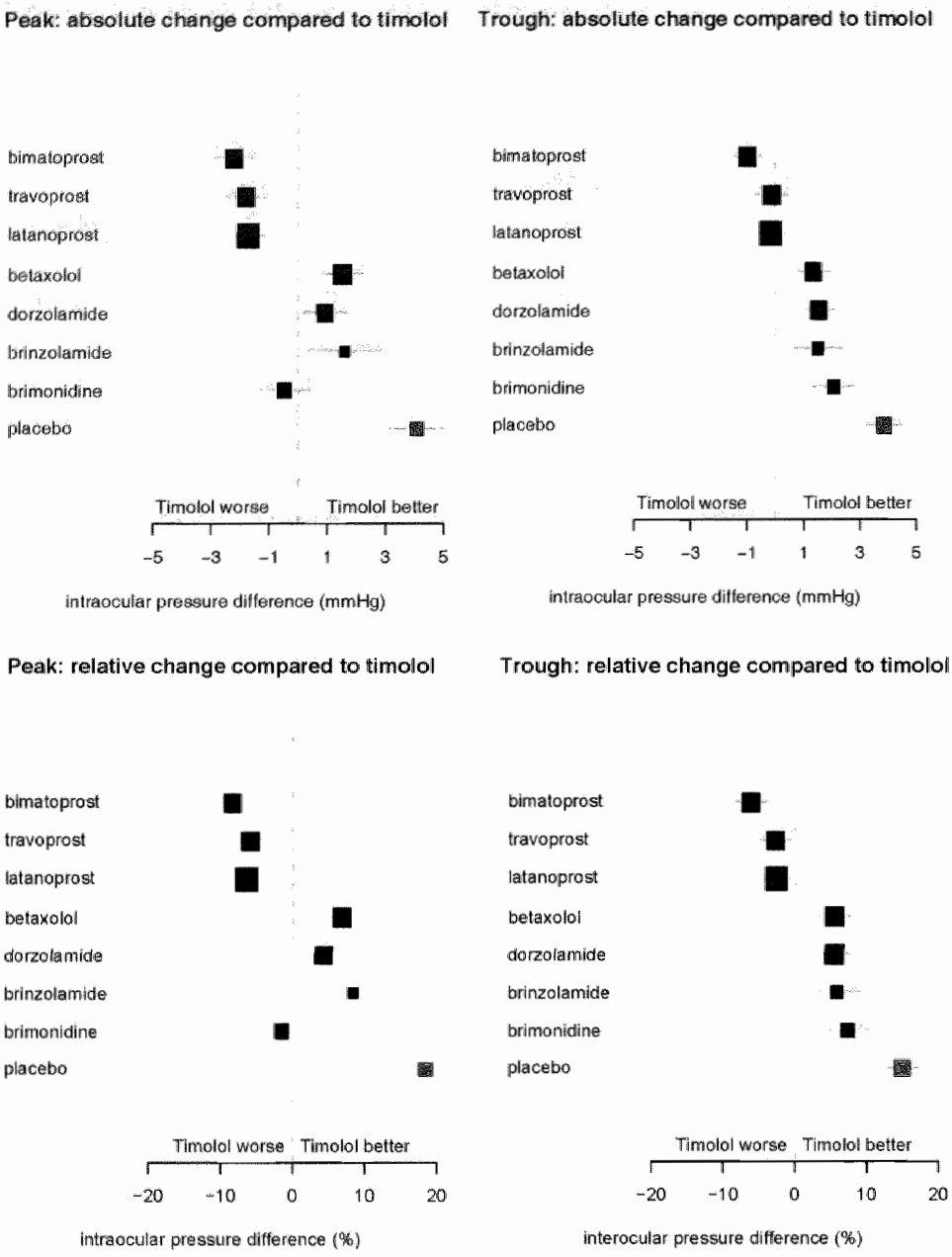

Figure 1. Forest plots of IOP reduction reached by starting glaucoma monotherapy, compared to timolol

In this analysis was tested for differences in IOP lowering capacity of all commonly used glaucoma drugs in comparison with timolol. The ranking presented is based on the differences in IOP reduction with timolol. If one of the other drugs had been used as reference the ranking would have been the same.

In this network meta-analysis incoherence is small and estimations from direct and indirect comparisons were similar: this implies that using the technique is suitable for these data and strengthens the choice for network meta-analysis.[2,3]

In general differences are small as can be judged by similar results as in our previous meta-analysis. However, results of network meta-analysis seem to be more consistent. This is illustrated by the example of bimatoprost which in conventional meta-analysis seems to be less potent than timolol at trough moment as looking at absolute reductions, while it was judged as more potent than timolol when judged from relative reductions.[1] In network meta-analysis the ranking as judged from absolute or relative reductions is the same.

In conclusion, we believe that the results of this network meta-analysis which makes optimal use of all available data presents the best available evidence of the rank order in IOP reductions achieved with all commonly used glaucoma drugs. Network meta-analysis shows that indirect comparison of these drugs is reliable, based on an analysis of incoherence estimates. There is a rank order in glaucoma medications, but differences compared to timolol seem to be small.

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4

Intraocular pressure lowering effects of adding dorzolamide or latanoprost to timolol - a meta-analysis of randomized clinical trials -

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Abstract

Objective: To estimate the intraocular pressure lowering effect of 2% dorzolamide or 0.005% latanoprost when added to 0.5% timolol.

Design: Meta-analysis of randomized clinical trials.

Participants: 17 articles reporting on 19 study arms with 5 possible treatment combinations and 4 study arms serving as controls.

Methods: Articles written in English, German, French or Dutch and published up to December 2004 were identified in Medline, Embase, the Cochrane Controlled Trials Register and references from relevant articles. Over 85% of the patients had to have primary open-angle glaucoma or ocular hypertension. The pooled 1 to 3 month additional intraocular pressure lowering effect after a run-in phase on timolol was calculated by performing meta-analysis using the random effects model.

Main Outcome Measures: Absolute and relative change in intraocular pressure after run-in on timolol, for peak moment, trough moment or mean diurnal curve.

Results: The pooled change from baseline (mean (95% confidence interval)) for 0.5% timolol varied from -0.7 mmHg (-1.2 to -0.2, mean diurnal curve) to -2.0 mmHg (-1.3 to -2.7, peak). The pooled change for 2% dorzolamide in concomitant use with 0.5% timolol was -4.1 mmHg (-4.4 to -3.8) at trough and -4.9 mmHg (-5.3 to -4.5) at peak. The fixed 2% dorzolamide and 0.5% timolol combination resulted in a pooled change of -3.8 mmHg (-4.2 to -3.4) at trough and -4.9 mmHg (-5.3 to -4.5) at peak. The concomitant use of 0.005% latanoprost and 0.5% timolol gave a pooled change from baseline of -6.0 mmHg (-6.8 to -5.2) at the mean diurnal curve. The fixed combination of 0.005% latanoprost and 0.5% timolol resulted in a mean change of -3.0 mmHg (-3.8 to -2.2) at the mean diurnal curve.

Conclusion: Adding either dorzolamide or latanoprost to timolol leads to an additional decrease in IOP. Due to the inclusion of patients with high untreated IOP and patients who are less responsive to timolol the exact magnitude of the decrease, and the patients to whom it applies remain obscure. It is of great importance to the ophthalmologist to know the additional IOP lowering effect of dorzolamide and latanoprost in patients who do respond to timolol and need additional lowering of IOP.

Introduction

Primary open-angle glaucoma (POAG) is a multifactorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve.[1] Major outcome studies have shown that lowering intraocular pressure (IOP) is beneficial in POAG[2] and ocular hypertension (OH).[3] This refers to both the risk of developing POAG in case of OH or progression in case of POAG. Moreover, one will aim at a low target IOP, and consequent large IOP reduction in cases of advanced glaucoma. A recent meta-analysis on the IOP lowering effect of glaucoma drugs showed a maximum mean IOP reduction of 33% from baseline IOP in case of monotherapy.[4] With the availability of newer classes of glaucoma drugs (alpha$_2$-adrenergic agents, carbonic anhydrases inhibitors, prostaglandin analogues and prostamide) the number of possible topical combination therapies has increased almost dramatically. The advantages of combining drugs are obvious. Additional lowering of IOP will increase the possibility of obtaining the aimed for target IOP. Furthermore a better 24 hour IOP profile can be reached. On the other hand, increasing the number of drugs has disadvantages as well. There is a risk of washing the first drug out of the conjunctival cul-de-sac with the following one and there is an increased exposure to preservatives. Finally inconvenience, side-effects and impact on quality of life can lead to non-compliance. Part of these disadvantages can be precluded by using fixed combinations.

The possibility to reach a lower target IOP with combined medical therapy has led us to conduct a meta-analysis on the IOP lowering effect of 2% dorzolamide or 0.005% latanoprost when added to 0.5% timolol drops bid. The choice for these two drugs was also made because of the commercially availability of the fixed combinations dorzolamide/timolol (Cosopt®) and latanoprost/timolol (Xalacom®). In this meta-analysis we studied peak and trough effects for the concomitant as well as the fixed combined use of these drugs. Furthermore we looked for possible methodological determinants that affect the interpretation of results.

Methods

For a complete and detailed description of the methods used for this meta-analysis we refer to the paper of van der Valk et al.[4] To summarize, potentially eligible for inclusion in our meta-analysis were randomized clinical trials on IOP lowering drugs, written in English, French, German or Dutch. In addition, for the meta-analysis on combined therapy we have extended our search for papers published up to December 2004. A first and rough judgement and consequent exclusion of articles was based on title, abstracts and medical subject heading. Of the remaining identified publications, the complete papers were printed or photocopied and studied after which non-randomized clinical trials were excluded. The potentially eligible randomised clinical trials served as a starting point for further selection based upon the criterion that at least one arm of the study had to report on the combined (concomitant or fixed) use of either 2%

dorzolamide and a beta-blocker or on 0.005% latanoprost and a beta-blocker. These papers served as a pool from which the definite selection took place. The main inclusion criterion was formulated as follows. Studies to be included had to report on the IOP lowering results of either adding 2% dorzolamide bid, 2% dorzolamide tid or 0.005% latanoprost qd (to be used in the evening) to 0.5% timolol bid after a run-in phase on 0.5% timolol bid or the switch to the fixed dorzolamide/timolol bid combination (Cosopt®) or the fixed latanoprost/timolol qd (to be used in the morning) combination (Xalacom®) again after a run-in phase on 0.5% timolol bid.

Data of included papers were extracted using a standard form. Operationalization of the items on this form was achieved by consensus meetings of three researchers (CABW, RvdV, JSAGS), before the beginning of the process of data abstraction.

The statistical analysis has been described in the meta-analysis on monotherapy.[4] The outcome measure was the change in IOP at peak and/or trough moment. The standard time point of measurement was 1 month or as an alternative the closest time point thereafter with a maximum of 3 months from baseline. Baseline was defined as the time point after a run-in phase of at least 2 weeks on 0.5% timolol bid. Peak and trough moments for each medication were as defined by the American Academy of Ophthalmology.[1] Seven publications did not report on separate peak or trough moments, just means of several measurements over the day, in the literature often addressed as mean diurnal curve (DC). The IOP results at peak (10:30 am) and trough (08:30 am) of one paper reporting on adding 2% dorzolamide tid to 0.5% timolol bid were merged with the results of the papers reporting on adding 2% dorzolamide bid to 0.5% timolol bid.

Results

Study eligibility

Of the 2175 selected abstracts published up to December 2004, 1345 were found obviously ineligible for inclusion due to a variety of reasons (e.g. studies on healthy subjects or animals). Of the 830 retrieved papers another 384 were excluded because these articles reported on non-randomized clinical trials. Of the remaining 446 articles, 74 were selected that reported on adding 2% dorzolamide or 0.005% latanoprost to beta blocker therapy. From these, 57 had to be excluded for reasons summarized in table 1. So after the completed selection process 17 papers were accepted that met our inclusion criteria.[5-21]

Table 1. Reasons for exclusion of 57 papers on beta-blocker use and adding either 2% dorzolamide or 0.005% latanoprost

Reason for exclusion (N)
No run in period (N=12)
Run in period, however not on 0.5% timolol bid (N=8)
More than 15% of included patients had other diagnosis than POAG or OH (N=7)
Only short term (<1 month) results reported (N=6)
Cross-over design without reporting separate results before crossing over (N=6)
IOP not primary outcome of the study (N=5)
No original data or review paper (N=5)
Unusual dosing or time point of dosing (N=2)
Miscellaneous (N=6)

The arms included 14 trough measurements (1526 subjects), 12 peak measurements. These 17 articles reported on 19 arms with 5 possible treatment combinations after run in on 0.5% timolol bid: adding 2% dorzolamide bid (6 arms), adding 2% dorzolamide tid (1 arm), switching to the fixed combination of dorzolamide/timolol bid (7 arms), adding 0.005% latanoprost qd (3 arms) or switching to the fixed combination of latanoprost/timolol qd (2 arms). Furthermore, 4 arms that continued 0.5% timolol bid (with or without placebo, dependent on the study design) were included as well (1478 subjects) and 9 mean diurnal curves (841 subjects). The baseline characteristics of the included study arms are shown in tables 2 to 7.

IOP lowering

Table 8 presents the mean absolute and relative IOP change from baseline and the 95% confidence intervals of 2% dorzolamide or 0.005% latanoprost when added to 0.5% timolol. As a control group the same results are presented for 0.5% timolol with or without placebo.

The pooled change from baseline for 0.5% timolol varied from -0.7 mmHg (-1.2 to -0.2 mmHg; -3.0% (-5.2 to -0.7%), mean diurnal curve) to -2.0 mmHg (-1.3 to -2.7 mmHg;-8.7% (-6.0 to -11.4%), peak). The pooled mean change for 0.5% timolol irrespective of the time point of measurement was -1.3 mmHg (-2.0 to -0.5 mmHg; -5.3% (-8.1 to -2.4%)).

The pooled change for 2% dorzolamide in concomitant use with 0.5% timolol was -4.1 mmHg (-4.4 to -3.8 mmHg; -16.7% (-19.2 to -14.2%), trough) and -4.9 mmHg (-5.3 to -4.5 mmHg; -20.2% (-21.2 to -19.2%), peak). The fixed 2% dorzolamide and 0.5% timolol combination resulted in a pooled change of -3.8 mmHg (-4.2 to -3.4 mmHg; -15.2% (-16.9 to -13.4%), trough) and -4.9 mmHg (-5.3 to -4.5 mmHg; -20.1% (-21.6 to -18.6%), peak). The overall pooled change

from baseline for 2% dorzolamide added to 0.5% timolol irrespective of concomitant or fixed use was -3.9 mmHg (-4.2 to -3.6 mmHg; -15.7% (-17.2 to -14.3%), trough) and -4.9 mmHg (-5.2 to -4.6 mmHg; -20.1% (-21.1 to -19.2%), peak).

The concomitant use of 0.005% latanoprost and 0.5% timolol gave a pooled change from baseline of -6.0 mmHg (-6.8 to -5.2 mmHg; -26.9% (-32.7 to -21.1%), mean diurnal curve). The fixed combination of 0.005% latanoprost and 0.5% timolol resulted in a mean change of -3.0 mmHg (-3.8 to -2.2 mmHg; -13.4% (-16.0 to -10.8%), mean diurnal curve).

Discussion

This meta-analysis of randomized clinical trials studied the IOP lowering effect of 2% dorzolamide bid/tid or 0.005% latanoprost qd when added to 0.5% timolol bid. The mean additional IOP change for 2% dorzolamide varies from -3.9 mmHg (-4.2 to -3.6 mmHg; -15.7% (-17.2 to -14.3%)) at trough to -4.9 mmHg (-5.2 to -4.6 mmHg; -20.1% (-21.1 to -19.2%)) at peak and for 0.005% latanoprost from -3.0 mmHg (-3.8 to -2.2 mmHg; -13.4% (-16.0 to -10.8%)) for the fixed combination to -6.0 mmHg (-6.8 to -5.2 mmHg; -26.9% (-32.7 to -21.1%)) at the mean diurnal curve for the concomitant use.

In order to make extrapolation of the results to everyday practice more securely we selected only studies that included patients with POAG or OH in at least 85% of cases. Other reasons for excluding papers were mainly because of study design. Twelve papers were excluded because there was no run in period. In these articles only newly diagnosed patients or patients who were on medication but have been completely washed out, were included. Eligible patients are then started on 2% dorzolamide or 0.005% latanoprost combined with 0.5% timolol. This design will only reveal results of the total IOP change of the combination and not on the additional IOP change of either latanoprost or dorzolamide. Studies with a cross-over design, not reporting on IOP change before cross over were excluded as well. And finally studies reporting on patients who had a run-in period on medication other than 0.5% timolol bid were excluded.

The time point of measurement was 1 month or the closest time point thereafter with a maximum of 3 months from baseline. This time point was chosen so that there is ample time for the drug to lower IOP while the number of cases lost to follow up is most likely small. The number of withdrawals in tables 2 to 6 is based on the published numbers after finishing the complete studies. Therefore, the numbers that were used to calculate the IOP changes at the chosen time points are presented as well. Whenever available, results of the intention-to-treat analysis was used in our calculations of changes in IOP. The number of patients used for the 1 to 3 months analysis on changes in IOP is therefore almost always larger than the baseline number of patients reduced with the withdrawal number.

Table 2. Baseline characteristics of 0.5% timolol bid and 2% dorzolamide tid concomitant combination

Trial	Run-in length (weeks)	Patients at baseline (N)	With-drawals (%)	Sex (M/F)	Mean age (y)	POAG (%)	OH (%)	Others (%)	Endpoint measurement (months)	Baseline IOP (SD) mmHg	Trough, hours after applying (N)	Peak, hours after applying (N)	Diurnal curve, hours after applying (N)
Strohmaier et al., 1998	2	121	9.1†	71/50	62	83†	17†		1	26.1 (3.8)	0/0 (121)		
Hutzelmann et al., 1998	2	148	3.4	48/100	64	100			1	25.3 (3.2)	0/0 (148)		
Michaud et al., 2001	3	109	7.3	48/61	na	63	30	6	1	25.8 (2.2)	0/0 (107)		
Emmerich et al., 2000	2-4	93	3.2	36/57	64	98	0	2	3	22.0 (2.5)	8/8 (90)		
Strohmaier et al., 1998	2	121	9.1†	71/50	62	83†	17†		1	25.0 (3.7)		2/2 (120)	
Hutzelmann et al., 1998	2	148	3.4	48/100	64	100			1	24.5 (3.2)		2/2 (148)	
Michaud et al., 2001	3	109	7.3	48/61	na	63	30	6	1	24.1 (1.9)		2/2 (106)	
Emmerich et al., 2000	2-4	93	3.2	36/57	64	98	0	2	3	22.3 (2.2)		2/2 (90)	
Hommer et al., 2003	2	48	6.3	19/29	65	56	25	15	3	nr (nr)			0/0, 2/2, 6/6, 8/8 (38)
Polo et al., 2002	>2	17	0	5/12	66	94	0	6	3	22.4 (4.9)			nr (16)
AISG, 2000	2-4	75	5.3	nr	nr	nr	nr	nr	3	23.0 (2.5)			nr (71)

nr = not reported, *median age, † not specified per treatment arm

Table 3. Baseline characteristics of 0.5% timolol bid and 2% dorzolamide tid fixed combination

Trial	Run-in length (weeks)	Patients at baseline (N)	With-drawals (%)	Sex (M/F)	Mean age (y)	POAG (%)	OH (%)	Others (%)	Endpoint measurement (months)	Baseline IOP (SD) mmHg	Trough, hours after applying (N)	Peak, hours after applying (N)	Diurnal curve, hours after applying (N)
Clineschmidt et al., 1998	3	104	9.6	42/62	64	75†	20†	5†	1	25.5 (3.4)	0/0 (102)		
Strohmaier et al., 1998	2	121	9.1†	50/71	61	83†	17†		1	26.1 (3.0)	0/0 (121)		
Honrubia et al., 2002	3-6	112	8.9	37/75	63	91	1	8	3	22.9 (1.9)	9/9 (102)		
Hutzelmann et al., 1998	2	151	1.3	65/86	63		100		1	25.6 (3.1)	0/0 (151)		
Coleman et al., 2003	>2	87	5.7	30/57	64*	49	45	6	1	24.8 (2.5)	0/0 (82)		
Sall et al., 2003	3	144	18.8	67/77	65	76	25	0	1	25.1 (3.3)	0/0 (141)		
Solish et al., 2004	3	242	7.4	98/144	64	76	22	4	1	24.7 (3.4)	0/0 (231)		
Clineschmidt et al., 1998	3	104	9.6	42/62	64	75†	20†	5†	1	25.5 (3.9)		2/2 (103)	
Strohmaier et al., 1998	2	121	9.1†	50/71	61	83†	17†		1	25.1 (3.3)		2/2 (120)	
Honrubia et al., 2002	3-6	112	8.9	37/75	63	91	1	8	3	23.2 (1.7)		2/2 (102)	
Hutzelmann et al., 1998	2	151	1.3	65/86	63		100		1	24.7 (3.2)		2/2 (151)	
Coleman et al., 2003	>2	87	5.7	30/57	64*	49	45	6	1	23.2 (3.0)		2/2 (82)	
Sall et al., 2003	3	144	18.8	67/77	65	76	25	0	1	24.4 (2.8)		2/2 (138)	
Solish et al., 2004	3	242	7.4	98/144	64	76	22	4	1	24.0 (2.7)		2/2 (224)	

nr = not reported, *median age, † not specified per treatment arm

Table 4. 0.5% timolol bid and 0.005% latanoprost qd concomitant

Trial	Run-in length (weeks)	Patients at baseline (N)	With-drawals (%)	Sex (M/F)	Mean age (y)	POAG (%)	OH (%)	Others (%)	Endpoint measurement (months)	Baseline IOP (SD) mmHg	Trough, hours after applying (N)	Peak, hours after applying (N)	Diurnal curve, hours after applying (N)
Bron et al., 2001	>2	19	10.5	8/11	69	74	21	5	1.5	23.2 (4.1)	0* (17)	12* (17)	
Bucci, 1999	2-4	49	8.2	21/28	59	88	0	12	3	21.4 (2.8)			2/12, 5/17, 9/22 (45)
Diestelhorst et al., 2000	2-4	121	3.3	51/70	62		100		3	23.3 (2.8)			2/12, 6/16, 8/18 (104)

nr = not reported, * trough for timolol and peak for latanoprost

Table 5. 0.5% timolol/0.005% latanoprost qd fixed combination

Trial	Run-in length (weeks)	Patients at baseline (N)	With-drawals (%)	Sex (M/F)	Mean age (y)	POAG (%)	OH (%)	Others (%)	Endpoint measurement (months)	Baseline IOP (SD) mmHg	Trough, hours after applying (N)	Peak, hours after applying (N)	Diurnal curve, hours after applying (N)
Pfeiffer, 2002	2-4	140	10.0*	67/73	64	76	19	5	3	21.6 (3.8)			0, 2, 8 (140)
Higginbotham., 2002	2-4	138	9.4	67/71	61	70	26	4	3	23.1 (3.8)			0, 2, 8 (138)

* not specified per treatment arm

Table 6. 0.5% timolol bid with or without placebo

Trial	Run-in length (weeks)	Patients at baseline (N)	With-drawals (%)	Sex (M/F)	Mean age (y)	POAG (%)	OH (%)	Others (%)	Endpoint measurement (months)	Baseline IOP (SD) mmHg	Trough, hours after applying (N)	Peak, hours after applying (N)	Diurnal curve, hours after applying (N)
Clineschmidt et al., 1998	3	98	9.2	47/51	63	75*	20*	5*	1	25.2 (3.1)	0 (98)		
Bron et al., 2001	>2	16	0.0	8/8	62	69	31	0	3	24.2 (3.6)	0 (16)		
Clineschmidt et al., 1998	3	98	9.2	47/51	63	75*	20*	5*	1	24.3 (3.6)		2 (95)	
Pfeiffer, 2002	2-4	149	10.0*	52/97	64	79	14	7	3	22.5 (4.1)			0, 2, 8 (149)
Higginbotham., 2002	2-4	140	25.7	80/60	63	70	24	6	3	23.7 (4.1)			0, 2, 8 (140)

* not specified per treatment arm

Table 7. Inclusion criteria with respect to medication and eligibility criteria for 17 studies included in the meta-analysis

Trial	Patients already on therapy included	Number of patients already on medication (%)	IOP (mmHg) criteria before run-in	IOP (mmHg) criteria after run-in	IOP (mmHg) before run-in (SD)
Hutzelmann et al., 1998	yes	nr	Eligibility	≥22 at trough and peak	nr
Hommer et al., 2003	yes	nr	On BB ≥ 22 or combination <22	Early morning IOP 22-28	nr
Polo et al., 2002	yes	100	On BB ≥ 22 if POAG or >27 if OH	None	nr
Michaud et al., 2001	yes	100	On timolol 23-36 (trough) and 21-36 (peak)	23-36 (trough) and 21-36 (peak)	nr
Emmerich et al., 2000	yes	100	On BB or combination ≥22 if POAG or >27 if OH	None	nr
AISG, 2000	yes	100	Uncontrolled on timolol	None	nr
Strohmaier et al., 1998	yes	nr	Eligibility	≥22 at trough and peak	nr
Clineschmidt et al., 1998	yes	nr	Eligibility	≥22 at trough and peak	nr
Honrubia et al., 2002	yes	100	Eligibility	≥21	nr
Coleman et al., 2003	yes	37	Eligibility	22- 34 at trough	nr
Sall et al., 2003	nr	nr	Eligibility	≥22 at peak	nr
Solish et al., 2004	yes	87	Eligibility	≥22 at peak	nr
Diestelhorst et al., 2000	yes	100	On BB >22 if POAG or >26 if OH	≥22 if POAG or >26 if OH	nr
Bron et al., 2001	yes	100	On BB or combination ≥21	None	nr
Bucci, 1999	yes	100	On BB inadequate IOP control	None	nr
Pfeiffer, 2002	yes	nr	≥25 with or ≥30 without therapy	None	27.0 (2.9)
Higginbotham., 2002	yes	85	≥25 with or ≥30 without therapy	None	nr

nr = not reported, BB = beta-blocker, POAG = primary open-angle glaucoma, OH = ocular hypertension

Table 8. Absolute and relative change for combinations and control

Generic group	Treatment combination	Concomitant/fixed	Time point	Absolute change (mmHg)		Relative change (%)		Number of studies
				Mean	CI	Mean	CI	
timolol and dorzolamide	0.5% timolol bid and 2% dorzolamide bid	concomitant	trough	-4.1	-4.4 to -3.8	-16.7	-19.2 to -14.2	4
	0.5% timolol bid and 2% dorzolamide bid	concomitant	peak	-4.9	-5.3 to -4.5	-20.2	-21.2 to -19.2	4
	0.5% timolol bid and 2% dorzolamide bid	concomitant	DC*	-3.8	-5.0 to -2.6	-17.8	-22.1 to -13.5	3
	0.5% timolol / 2% dorzolamide bid	fixed	trough	-3.8	-4.2 to -3.4	-15.2	-16.9 to -13.4	7
	0.5% timolol / 2% dorzolamide bid	fixed	peak	-4.9	-5.3 to -4.5	-20.1	-21.6 to -18.6	7
	0.5% timolol and 2% dorzolamide	concomitant or fixed	trough	-3.9	-4.2 to -3.6	-15.7	-17.2 to -14.3	11
	0.5% timolol and 2% dorzolamide	concomitant or fixed	peak	-4.9	-5.2 to -4.6	-20.1	-21.1 to -19.2	11
timolol and latanoprost	0.5% timolol bid and 0.005% latanoprost qd	concomitant	trough/peak†	-5.7	-4.0 to -7.4	-24.6	-17.4 to -31.8	1
	0.5% timolol bid and 0.005% latanoprost qd	concomitant	DC‡	-6.0	-6.8 to -5.2	-26.9	-32.7 to -21.1	2
	0.5% timolol / 0.005% latanoprost qd	fixed	DC§	-3.0	-3.8 to -2.2	-13.4	-16.0 to -10.8	2
control	0.5% timolol with or without placebo	not applicable	trough	-1.4	-2.9 to 0.1	-5.6	-11.5 to 0.3	2
	0.5% timolol with or without placebo	not applicable	peak	-2.0	-1.3 to -2.7	-8.7	-6.0 to -11.4	1
	0.5% timolol with or without placebo	not applicable	DC‖	-0.7	-1.2 to -0.2	-3.0	-5.2 to -0.7	2
	0.5% timolol	not applicable	trough/peak/DC‖	-1.3	-2.0 to -0.5	-5.3	-8.1 to -2.4	5

*one mean diurnal curve at 0, 2, 6, and 8 hours after timolol and dorzolamide and two mean diurnal curves of unknown time points
† 0 hour after timolol and 12 hours after latanoprost
‡ one mean diurnal curve at 2/12, 6/16 and 8/18 hours after timolol/latanoprost and one mean diurnal curve at 2/12, 5/17 and 9/22 hours after timolol/latanoprost
§ two mean diurnal curves at 0, 2, and 8 hours after fixed timolol/latanoprost
‖ two mean diurnal curves at 0, 2, and 8 hours after timolol

We choose to include studies on both the concomitant and fixed combined use. Comparing results of concomitant therapy to the fixed combination reveals little or no problems in case of dorzolamide. Patients on 0.5% timolol bid are advised to use the drops at relatively fixed daily time points (mostly 08:00 am and 08:00 pm). Peak (2 hours after using drops) and trough (0 hours before using drops) moments are obvious. In this respect nothing changes when dorzolamide is added or a switch is made to the fixed combination: peak and trough moments of timolol remain the same and coincidence with peak and trough moments of dorzolamide. With other variables being constant one will expect little or no differences in IOP changes between concomitant and fixed use. This is confirmed in our meta-analysis where at trough mean IOP change for concomitant use was -16.7% and for fixed use it was -15.2% while on peak it was respectively -20.2% and -20.1%. This comparison is much more difficult when latanoprost is added to timolol. Latanoprost will have a peak effect at 12 hours from the moment of dosing. Latanoprost qd (dosed in the evening) as concomitant therapy with timolol bid will lead to a peak effect in the morning, while for the fixed combination (dosed in the morning) this peak effect will occur at some time point in the afternoon or the evening. Most study arms (4 out of 5) on adding latanoprost to timolol therefore report on mean diurnal IOP curves, instead of peak and trough results. Despite this similarity in study design we found a rather large difference in IOP decrease for the concomitant use (additional 26.9% IOP decrease) versus the fixed use (additional 13.4% IOP decrease). An explanation is that in the studies on the fixed combination the mean diurnal curve was calculated from measurements at 0, 2 and 8 hours from the time point when the drops are used. This means that only one peak measurement for timolol and no peak measurements for latanoprost were included. In the concomitant studies IOP was measured at 2, 5-6 and 8-9 hours after timolol and 12, 16-17 and 18-22 hours after latanoprost. Here at least two peak moments for timolol and at least one peak moment for latanoprost were included.

Lowering IOP is beneficial both in OH and POAG. A recent meta-analysis of randomized controlled trials revealed that an IOP lowering strategy delays the progression of visual field deterioration.[2] The aimed for target IOP is often set to a level which is 20% to 30% lower than the untreated IOP. However, dependent on the glaucomatous damage and the presence of other risk factors the target IOP has sometimes to be chosen such that IOP lowering beyond 30% or even 40% is necessary.[1, 22] Combining either 2% dorzolamide or 0.005% latanoprost to 0.5% timolol will increase the possibilities for reaching these low target IOP levels.

The exact magnitude of the true additional IOP decreasing effect and the patients to whom this applies still remains obscure. This is illustrated as follows. Baseline IOP in the meta-analysis on monotherapy was defined as the IOP after adequate washout of all IOP lowering drugs and was 25.5 ± 1.2 mmHg (mean ± SD) for all included 0.5% timolol arms.[4] The baseline IOP in this meta-analysis however is defined as the IOP after a run-in period on 0.5% timolol bid for at least 2 weeks and is 24.5 ± 1.1 mmHg. Although statistically significant, the difference is remarkably small. Two most likely explanations can be offered.

The first explanation is that in these add-on studies preferably patients with high untreated IOP levels are included. Even after starting with timolol the IOP will then still be too high. Such a selection may have occurred because in all studies, except one, an IOP related inclusion criterion either before or after the run-in period was used. Especially in studies with patients already on medication one can assume that during regular outpatient visits prior to inclusion in the study, non-responders to the prescribed medication would have been identified. It is unlikely that they were included in the studies. Unfortunately only one study reported the untreated pre run-in IOP.[16] It is therefore not possible to verify how many patients had a high untreated IOP.

A second explanation is the possibility for including predominantly patients that are less responsive to timolol. If this is true, the results in this study would reflect more the treatment strategy of substitution of monotherapy than the addition of a second drug. Discrepancies in add-on studies with and those without a run-in period favor this explanation. Timolol will lead to a mean relative IOP decrease of 26% at trough and 27% at peak.[4] Adding dorzolamide will give an additional relative decrease of 16% at trough and 20% at peak and adding latanoprost will lead to a maximum additional mean diurnal curve IOP decrease of 13% for fixed combination use to 27% for concomitant use (data from this study). The theoretical total combined effect can be calculated from these figures. For example, timolol at trough will lead to a mean IOP decrease of 26%. Adding dorzolamide will lower the achieved IOP (74% of the initial IOP) further by 16%, resulting in a final IOP of 62% (84% of 74%) of the initial IOP. This would result for the timolol-dorzolamide combination in a relative IOP decrease of 38% from the initial IOP at trough. The same applied to dorzolamide at peak will lead to a total decrease of 42% and for the timolol-latanoprost combination a relative IOP decrease of 36% to 46%. In order to compare this to the published results on the total IOP decrease of combined therapy we selected 8 eligible papers that were originally excluded because they lacked a run-in phase on 0.5% timolol bid.[23-30] In these studies the total mean relative IOP decrease of the combination of 0.5% timolol and 2% dorzolamide varied at trough from 16.5% to 29.6% and at peak from 23.2% to 33.7%. For the fixed combination of timolol and latanoprost the relative IOP decrease varied from 25.2% to 36.7% at the mean diurnal curve (no data on the concomitant use of timolol and latanoprost are available). This empirical IOP decrease of timolol and dorzolamide or latanoprost is less than the calculated IOP decrease. The difference could be explained by a lower IOP reducing effect of timolol. One must therefore assume that patients less responsive to timolol are included in the trials with a run-in phase resulting in a relatively high additional IOP lowering, thereby limiting the application of the results to the patients of whom we wished to know the additional effect.

We conclude that adding either dorzolamide or latanoprost to timolol can lead to an additional decrease in IOP. In patients with high untreated IOP, advanced glaucoma damage or the necessity of a low target IOP combining drugs may be beneficial. However, in daily practice it is most likely that irrespective of the initial IOP one will start with monotherapy, evaluate and only in case of responsiveness in IOP and the necessity of a lower target IOP a second drug

will be added. From the results of this meta-analysis one must conclude that so far add-on studies on dorzolamide or latanoprost report on both patients with high initial IOP and low responsiveness to timolol.

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5

Predicting IOP change before initiating therapy: timolol vs latanoprost (the DURING study)

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Abstract

Purpose: To study intraocular pressure (IOP) reductions reached in clinical practice with timolol and latanoprost, taking into account indications, contraindications and risk factors, and to predict IOP reduction from these variables.

Patients and methods: Primary open-angle glaucoma (suspect) and ocular hypertension patients were recruited from nine Dutch centers. Mean absolute and relative IOP reductions were calculated for comparing timolol with latanoprost. IOP reduction was calculated comparing patients with certain indications, contraindications and risk factors to those without.

Results: 156 subjects started on timolol and 76 started on latanoprost monotherapy. Mean (95% confidence interval) absolute IOP reduction for timolol was 7.2 mmHg (7.9; 6.5) and 6.9 mmHg (8.0; 5.8) for latanoprost. Mean relative change (95% confidence interval) was 27.2% (29.3; 25.1) for timolol and 26.6% (30.2; 22.9) for latanoprost. No significant difference in IOP reduction between timolol and latanoprost was found when adjusting for indications, contraindications, and risk factors. At the time of starting treatment, none of these items normally used for the management of glaucoma, except IOP at baseline could predict change in IOP.

Conclusions: In clinical practice timolol and latanoprost achieve similar IOP reductions comparable to those achieved in randomized trials. No clinically relevant information for glaucoma management can be used to predict IOP reduction accurately.

Introduction

In open-angle glaucoma and ocular hypertension treatment, the most recent European guidelines leave the choice of an initial drug to the ophthalmologist.[1] The difference in intraocular pressure (IOP) reducing effect between drugs could be a guideline. A recently performed meta-analysis of randomized clinical trials (RCTs) shows no or only small differences in IOP reduction between the glaucoma drugs.[2] Drug use in everyday circumstances however may differ from the situation in a clinical trial due to the selection of patients and the experimental circumstances. Furthermore, incomplete reporting of outcomes with published articles of randomized trials is common.[3] We therefore studied the effectiveness of timolol and latanoprost in newly diagnosed patients in routine clinical practice. Furthermore, the aim was to study the influence of indications, contraindications, and risk factors on IOP reduction in primary open-angle glaucoma (POAG), primary open-angle glaucoma suspect (POAG suspect) and ocular hypertension (OH) patients. This study is part of the DUtch Research project on treatment outcome IN Glaucoma patients (DURING study).

Patients and methods

The DURING study was carried out in 9 Dutch hospitals, which included academic, teaching and non teaching hospitals. The study was approved by the local ethics committees. The purpose of this project was to collect data about the care of glaucoma patients in clinical practice who received or were to receive glaucoma medication. Written informed consent was asked from patients aged 18 years or over, who were able to read and write Dutch and to decide whether to participate or not. Patients enrolled in the study between March 2001 and January 2004.

Hospital staff registered data on the patient after receiving a written informed consent. The ophthalmologist recorded type of glaucoma. Research assistants trained in glaucoma research recorded all IOP measurements and medication, as well as all previous ocular operations and laser treatments.

The ophthalmologist recorded the reason why the patients were unwilling or unable to participate. These reasons were divided into five main categories: ocular (e.g. blind, low visual acuity), physical (e.g. too old, too sick), unmotivated to participate (e.g. no time, too busy), follow-up (e.g. plans to move out of area or to other hospital), and miscellaneous reasons (e.g. unknown reason).

Data on comorbidity were obtained from the general practitioner. The patient was asked about comorbidity if this information could not be obtained from the general practitioner after written and telephonic reminders.

For the current analysis we selected patients with POAG, POAG suspect or ocular hypertension who had started on timolol or latanoprost, with a maximum of three visits before enrolment in the DURING study.

Statistical analysis

Differences in binominal variables were tested using Chi^2-tests and t-tests were used for continuous variables. The absolute and relative IOP reductions were calculated as the difference from the IOP recorded at the start of drug usage and the first visit after that. This analysis has a power of 0.67 to detect a 4% or larger one-sided difference between latanoprost and timolol in IOP reduction. This 4% difference in peak IOP reduction between latanoprost and timolol is reported in a recently performed meta-analysis.[2] In most studies this value corresponds to a difference of 1 mmHg. To detect a 5% difference this power is 0.83.

The influence of indications, contraindications and risk factors was tested by means of linear regression analysis for the total group of patients who had started on timolol and latanoprost. POAG, POAG suspect, OH and IOP at baseline were considered indications for initiating treatment. As contraindications respiratory, cardiac, and musculoskeletal comorbidity and previous cataract surgery were analyzed.[3-7] As risk factors age, family history of glaucoma, diabetes mellitus, myopia (defined as a spherical equivalent of lower than –4), and gender were included.[1,8-11] After evaluating each single indication, contraindication and risk factor, the combined effect these variables on IOP reduction was evaluated.

For the analyses, comorbidity was categorized according to the International Classification of Primary Care (ICPC) main categories. The SAS 8.0 (Cary, NC) software was used for performing the analyses.

Results

In the DURING study between March 2001 and January 2004, 3841 patients were included. The response rate was 79%. Patients unwilling to participate were generally older and more frequently female. Frequencies of reasons for not participating are listed in table 1. The mean age ± standard deviation of included patients was 69 ± 12 year, range 21 to 97 years, 1920 (50%) were male.

The DURING study population included 232 patients who had newly diagnosed POAG, POAG suspect or OH and were started on timolol (n=156) or latanoprost (n=76) monotherapy. Data on comorbidity were available for 85% (198/232) of these patients. Ninety-three percent of the data on comorbidity were obtained from general practitioners. In table 2, prevalences are listed. Twenty percent of the patients had no comorbidity. Except for respiratory comorbidity, which was less frequently present in the timolol group, the distribution of indications, contraindications and risk factors was similar in both groups (table 2).

Table 1. Patient reasons for not participating in the DURING study

Reason	Number of patients
Ocular	43 (10%)
Physical	104 (23%)
Not motivated	167 (37%)
Follow-up	19 (4%)
Miscellaneous	114 (26%)
Total*	447 (100%)

* Data from 7 of the 9 participating centers

Table 2. Risk factors, indications, and contraindications at baseline of primary open-angle glaucoma (suspect) or ocular hypertension patients that started on timolol or latanoprost monotherapy

Baseline characteristic	Timolol (n=156)	Latanoprost (n=76)	*P* value difference between treatments
	Number/total (%)	Number/total (%)	
Risk factors:			
Family history of glaucoma	37/156 (24%)	21/76 (27%)	0.52
Myopia	13/156 (16%)	2/76 (5%)	0.07
Diabetes Mellitus	19/134 (14%)	5/64 (8%)	0.20
Gender	84/156 (54%)	40/76 (53%)	0.86
Age ± SD (years)	65.7 ± 10.7	67.1 ± 13.1	0.39
Indications:			
$IOP_{baseline}$ ± SD (mmHg)	25.3 ± 4.9	24.3 ± 5.2	0.14
Diagnosis			0.33
POAG	99/156 (63%)	51/76 (67%)	
POAG suspect	14/156 (9%)	10/76 (13%)	
Ocular hypertension	43/156 (28%)	15/76 (20%)	
Contraindications:			
History of cataract surgery	8/156 (5%)	7/76 (9%)	0.24
Cardiac comorbidity	67/134 (50%)	38/64 (59%)	0.22
Respiratory comorbidity	8/134 (6%)	10/64 (16%)	0.03
Musculoskeletal comorbidity	14/134 (10%)	8/64 (13%)	0.67
Other:			
No comorbidity	26/134 (19%)	14/64 (22%)	0.69
Other comorbidity	31/134 (23%)	8/64 (13%)	0.08

The mean (95% CI) absolute IOP reduction for timolol was 7.2 mmHg (7.9; 6.5) and for latanoprost 6.9 mmHg (8.0; 5.8), corresponding with a difference (95% CI) of 0.3 mmHg (-1.5; 0.9) between timolol and latanoprost. Relative reductions (95% CI) were 27.2% (29.3; 25.1) and 26.6% (30.2; 22.9) respectively, corresponding with a difference (95% CI) of 0.6% (-4.5; 3.3). Absolute and relative differences in reduction of IOP between timolol and latanoprost did not change substantially, and were - 0.1 mmHg, (95% CI: -1.6; 1.4), and 0.54 %, (95% CI: -5.2; 6.2) respectively, after adjustment for the indications,

contraindications and risk factors: age, gender, baseline IOP, family history of glaucoma, myopia, previous cataract surgery, respiratory, cardiac, musculoskeletal, other, or no comorbidity.

Baseline IOP was the only predictive factor for IOP reduction. The other variables were poor predictors of change in IOP (table 3).

Table 3. Regression coefficients (95% CI) for baseline characteristics for relative and absolute change in IOP from baseline of the combined timolol and latanoprost group in primary open-angle glaucoma (suspect) or ocular hypertension patients

	Relative IOP change (%) and 95% -confidence interval*	**Absolute IOP change (mmHg) and 95% -confidence interval***
Risk factors:		
Family history of glaucoma (no = reference)	2.7 (-1.6; 6.9)	0.4 (-0.9; 1.7)
Myopia (no = reference)	1.4 (-6.8; 9.6)	0.7 (-1.8; 3.3)
Age (per 10 years)	-0.2 (-1.8; 1.4)	-0.04 (-0.5; 0.5)
Diabetes Mellitus (no = reference)	3.9 (-2.3; 10.1)	0.9 (-1.0; 2.8)
Gender (female = reference)	4.1 (0.5; 7.8)	1.0 (-0.1; 2.1)
Indications:		
IOP at baseline (per mmHg)	-1.4 (-1.7; -1.1)	-0.6 (-0.7; -0.5)
POAG suspect (vs POAG)	4.4 (-1.8; 10.5)	1.3 (-0.5; 3.2)
Ocular hypertension (vs POAG)	1.2 (-3.1; 5.5)	-0.4 (-1.7; 0.9)
Contraindications:		
History of cataract surgery (no = reference)	-2.9 (-10.3; 4.6)	-1.1 (-3.4; 1.2)
Cardiac comorbidity (no = reference)	0.9 (-3.2; 5.0)	0.5 (-0.8; 1.7)
Respiratory comorbidity (no = reference)	-3.7 (-10.8; 3.3)	-1.3 (-3.5; 0.9)
Musculoskeletal comorbidity (no = reference)	2.1 (-4.3; 8.6)	1.1 (-0.9; 3.1)
Other:		
Latanoprost (no = reference)	0.6 (-3.3; 4.5)	0.3 (-0.9; 1.5)
No comorbidity (no = reference)	-2.1 (-7.2; 2.9)	-0.8 (-2.4; 0.7)
Other comorbidity (no = reference)	2.6 (-2.5; 7.7)	0.5 (-1.0; 2.1)

*negative value indicates more decrease in IOP after treatment in presence of a factor compared to the absence of a factor, or with increasing value of characteristic.

Discussion

The results of our analysis based on clinical practice data, indicate that timolol and latanoprost achieve similar reductions in IOP. These results remained unchanged after adjustment for potential confounding factors. Moreover, the IOP reductions observed in clinical practice are similar to those typically observed in RCTs.[2] IOP at baseline was the only significant predictor for change in IOP in the total group and also in the latanoprost or timolol group analyzed separately (data not shown). In clinical practice the magnitude of IOP reduction cannot be predicted by indications, contraindications or risk factors for glaucoma.

For this study, patients were identified in 9 Dutch centers (academic, teaching and non-teaching hospitals) thereby reducing selection bias. The participation rate in this study was high (79%). Only a minority (10%) of the non participants had ocular reasons not to participate.

The percentage of patients with data on comorbidity in this analysis was 85%, 93% of which were supplied by the general practitioner. In The Netherlands the general practitioner delivers continuous care and acts as a gatekeeper to other health care facilities.[12] We therefore are confident that these data are complete and of good quality.

Interestingly, the reductions in IOP for timolol and latanoprost are fully comparable to those observed in RCTs.[2] In clinical practice, selection of patients is based on indication criteria and contraindication criteria. For example, indications for starting therapy in OH are the presence of risk factors for glaucoma, implying that treatment should also be started in patients with only moderately increased IOP but in the presence of risk factors. Contraindications are other diseases that give an increased risk of adverse effects, e.g. respiratory disease in patients receiving timolol,[6] or drug interactions, e.g. non-steroidal anti-inflammatory drugs which may interfere with IOP reduction by latanoprost.[13]

These indications, contraindications and risk factors are assessed by the ophthalmologist, and used for the management of OH and glaucoma patients. If any IOP reduction had been different between timolol and latanoprost, or different from the situation in RCTs, these differences could have been explained by differences in indications, contraindications and risk factors. However, we have shown that they did not lead to a difference in treatment effect.

In summary, our results support the absence of a preference for either timolol or latanoprost for initiating treatment in POAG, POAG suspect and OH patients when IOP reduction is considered. Moreover, the expected IOP reduction is not different for patients who differ in indications, contraindications or risk factors. The latter implies that it cannot be predicted which patient will respond respectively more or less to these drugs.

Our results give empirical support for the European guidelines for the initial treatment.[1] Preference for either timolol or latanoprost can not be based on their effect on IOP lowering. Moreover, we have shown that there is no empirical evidence that one should not start treatment with either drug in some patient groups, based on data relevant for and gathered in daily practice for the management of OH and POAG.

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6

Changes in process and outcome of glaucoma treatment after the introduction of new glaucoma medication

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Abstract

Purpose: To describe changes in process and outcome of glaucoma treatment over the period 1995-2002, 4 years before and 4 years after new glaucoma drugs became available (January 1999).

Methods: An observational study was conducted in primary open-angle glaucoma (suspect), and ocular hypertension patients who had started medical treatment in 1995 or thereafter. The processes of starting, changing and intensifying medical treatment in general, and in patients with contraindications to beta-blockers before and after January 1999 were described. As outcomes, the change in mean IOP and the percentage of patients achieving an intraocular pressure below 18 or 22 mmHg were calculated.

Results: After January 1999 a shift from starting on betaxolol to hypotensive lipids took place. This shift was more pronounced in patients with respiratory comorbidity. The percentage of patients starting on timolol did not differ between both periods. After January 1999 therapy was changed more often, in the first two visits compared to the period before January 1999 (38% vs. 27%, $p<0.0001$). In more recent years a larger percentage of glaucoma patients were treated with 2 or more drugs (34% in 2002 vs. 13% in 1995). Over the period 1995-2002, baseline IOP did not change ($p=0.85$), for mean IOP at visit 4 a trend to lower IOPs was observed ($p< 0.0001$). More patients achieved an IOP level under 22 and 18 mmHg after January 1999 than before, 85% vs. 77%, and 46% vs. 33% respectively ($p<0.0001$).

Conclusion: This study shows a change in process and improvement in outcome of glaucoma treatment after new glaucoma drugs had become available.

Introduction

The value of new drugs can not always be assessed by comparing them in a randomized clinical trial. In the case of new glaucoma drugs for example, differences in intraocular pressure (IOP) lowering effects are small in randomized clinical trials and sometimes even absent in clinical practice.[1, 2] On the other hand, the number of glaucoma operations has almost halved since the introduction of new glaucoma drugs.[3-6] This discrepancy suggests that these new glaucoma drugs do have an impact on the treatment of glaucoma, despite the relatively small differences in IOP reducing effect.

In general, new drugs lead to more options in initiating treatment in patients with contraindications for conventional drugs, in changing treatment in patients with side effects and in changing or combining drugs in case of insufficient intraocular pressure decrease. In this paper we describe the process and outcome of glaucoma treatment in the period before and following the introduction of new classes of glaucoma drugs.

Methods

Since January 1999, in the Netherlands, the costs of new glaucoma drugs are reimbursed and a treatment protocol for glaucoma is available. January 1999 therefore separates two time periods: before and after the general availability of new glaucoma drugs. For the analyses, we selected patients with primary open-angle glaucoma (suspect) or ocular hypertension who had started with medical glaucoma therapy on January 1st 1995 or thereafter.

This study was carried out in 9 Dutch hospitals, which included academic, teaching and non teaching hospitals. The study was approved by several ethical committees. Written informed consent was asked from patients aged 18 years or over, who were able to read and write Dutch and decide whether to participate. Patients were enrolled in the study between March 2001 and January 2004.

Hospital staff registered data on the patient after having received a written informed consent. The type of glaucoma was recorded by the ophthalmologist who initiated treatment. All IOP measurements, medication as well as all previous ocular surgeries and laser treatments were recorded from the medical files by research assistants trained in glaucoma research.

Comorbidity was categorized according to the International Classification of Primary Care (ICPC) main categories. Data on comorbidity were obtained from the general practitioner, who received written and telephonic reminders if necessary. The patients received a questionnaire if the general practitioner did not respond. Data on comorbidity were available for 82% (1273/1561) of the patients. Ninety-three percent of the data on comorbidity were obtained from general practitioners.

In this study, the process of glaucoma treatment comprised starting, changing and intensifying treatment. Starting treatment was studied both in regular patients as well as in those with respiratory comorbidity.

Changing therapy was defined as switching, adding or stopping drugs in the first or second visit after baseline. Laser or surgery were also considered change of therapy.

In the analyses for intensity of treatment, the fourth visit from baseline was used. This means that there had been three moments in which the therapy could have been changed. The fourth visit corresponds with a period of approximately one-and-a-half years. Furthermore, the percentage of patients on monotherapy, 2 drugs, or 3 or more drugs were calculated per year and plotted.

The outcome of glaucoma treatment was defined as mean IOP at the fourth visit to the ophthalmologist. This was calculated per year over the period 1995-2002, and for the period before and after January 1999. In addition, the percentage of patients who an IOP under the level of 22 mmHg or 18 mmHg is calculated.

Differences in categorical characteristics between the patients who had started medical glaucoma therapy before January 1999 and the patients who had started therapy after January 1999 were calculated by Chi^2-tests, and for continuous variables by t-tests. A linear regression analyses was performed to test for a linear trend over the years in baseline IOP, and in IOP after 4 visits. All analyses were performed using the SAS 8.0 software (Cary, NC, USA).

Results

In this observational study, 79% of eligible patients participated. In total, 1561 were included, 551 patients had started before, and 1010 patients had started in or after January 1999. Baseline characteristics are presented in table 1.

Process of glaucoma treatment

Before January 1999, 92% (507/551) of the patients had started with beta-blocker monotherapy. After this moment 68% (685/1010) had started with beta-blocker monotherapy (table 1). The number of patients who had started with timolol was relatively stable 47% (259/551) before vs. 49% (490/1010) after January 1999. A larger change, from 21% (114/551) before, to 5% (49/1010) after January 1999 occurred in the group of the other non-selective beta-blockers. For the selective beta-blocker betaxolol these numbers were 24% (134/551), and 14% (146/1010) respectively. After January 1999, 22% (218/1010) had started with a hypotensive lipid (latanoprost, travoprost, bimatoprost).

Table 1. Patient characteristics and starting therapy of patients with primary open glaucoma (suspect) and ocular hypertension that started in 1995-2003

Baseline characteristic	1995-1998 (n=551)	1999-2003 (n=1010)	*P* value for difference between 1995-1998 and 1999-2003
	Number/total (%)	Number/total (%)	
Risk factors:			
Family history of glaucoma	121/551 (22%)	207/1010 (21%)	0.50
Myopia (SE < -4)	34/360 (9%)	61/607 (10%)	0.76
Diabetes Mellitus	49/430 (11%)	109/843 (13%)	0.43
Gender (male)	271/551 (49%)	502/1010 (50%)	0.84
Age ± SD (years)	69 ± 11	68 ± 11	0.11
Indications:			
$IOP_{baseline}$ ± SD (mmHg)	25.6 ± 5.8	25.8 ± 6.8	0.55
Diagnosis			0.64
POAG	401/551 (73%)	723/1010 (72%)	
POAG suspect	105/551 (19%)	190/1010 (19%)	
Ocular hypertension	45/551 (8%)	97/1010 (10%)	
Contraindications:			
Cataract surgery before initiation of treatment	18/551 (3%)	69/1010 (7%)	0.003
Cardiovascular comorbidity	169/430 (39%)	405/843 (48%)	0.003
Respiratory comorbidity	32/430 (7%)	91/843 (11%)	0.06
Musculoskeletal comorbidity	30/430 (7%)	80/843 (10%)	0.13
Other:			
No comorbidity	91/430 (21%)	195/843 (23%)	0.43
Other comorbidity	42/430 (10%)	141/843 (17%)	<0.0001
% *LTP ever performed*	89/551 (16%)	46/1010 (5%)	<0.0001
% Trabeculectomy ever performed	19/551 (3%)	16/1010 (2%)	0.02
% Iridectomy ever performed	16/551 (3%)	13/1010 (1%)	0.02
Starting therapy:			<0.0001
Betablockers			
Timolol	259/551 (47%)	490/1010 (49%)	
Metipranolol	13/551 (2%)	7/1010 (1%)	
Levobunolol	36/551 (7%)	17/1010 (2%)	
Carteolol	65/551 (12%)	25/1010 (2%)	
Betaxolol	134/551 (24%)	146/1010 (14%)	
Hypotensive lipids			
Latanoprost	5/551 (1%)	193/1010 (19%)	
Bimatoprost or Travoprost	0/551 (0%)	25/1010 (2%)	
Combination	21/551 (4%)	68/1010 (7%)	
Other	18/551 (3%)	39/1010 (4%)	

Before January 1999, 38% (12/32) of the patients with respiratory comorbidity had started with the selective beta-blocker betaxolol, after January 1999 this percentage was 13% (12/91). In this latter period 41% (37/91) of the patients with respiratory comorbidity had started with a hypotensive lipid. This shows that patients with respiratory comorbidity were generally treated with drugs that are more potent in IOP reduction.

Patients who had started after January 1999 more often changed therapy at their first and/or second visit compared to the period before January 1999, 38% (386/1008) and 27% (117/434) respectively (p <0.0001) (table 2).

Table 2. Frequencies of POAG (suspect) and ocular hypertension patients that changed therapy 1 or 2 visits after initiating therapy and frequency of patients that did not change therapy

Intervention	Total	1995-1998	1999-2003
No change	949 (66%)	317 (73%)	632 (62%)
Monotherapy to monotherapy	207 (14%)	37 (8%)	170 (17%)
Monotherapy to combination therapy	164 (11%)	36 (8%)	128 (13%)
Combination therapy to combination therapy	24 (2%)	6 (1%)	18 (2%)
Combination therapy to monotherapy	21 (1%)	5 (1%)	16 (2%)
Stop medical therapy	40 (3%)	11 (3%)	29 (3%)
Laser trabeculoplasty	25 (2%)	16 (4%)	9 (1%)
iridectomy	7 (0.5%)	3 (1%)	4 (0%)
trabeculectomy	5 (0.5%)	3 (1%)	2 (0%)
Total	1442 (100%)	434 (100%)	1008 (100%)

The percentage of patients on 1, 2, or 3 drugs and over at the fourth visit from baseline for the years 1995 to 2002 is described in figure 1. A trend to more intensive treatment over the years, after introduction of the newer classes of glaucoma drugs is observed (figure 1).

Outcome of glaucoma treatment

The mean baseline IOP did not change statistically significant over the years. The mean IOP after 4 visits showed a statistically significant decreasing trend over the years (p<0.0001) (table 3). The overall mean IOP (± standard deviation) before January 1999 was 19.1 (± 3.7) mmHg and after January 1999 17.9 (± 4.0) mmHg, the difference (95%-confindence interval) in IOP reduction between these periods was 1.2 mmHg (0.8; 1.7).

The mean percentage (over the first 10 visits) of patients that achieved an IOP under 22 mmHg was 77% before January 1999, and 83% thereafter. Thirty-three percent achieved an IOP under 18 mmHg before January 1999, and 46% thereafter (figure 2).

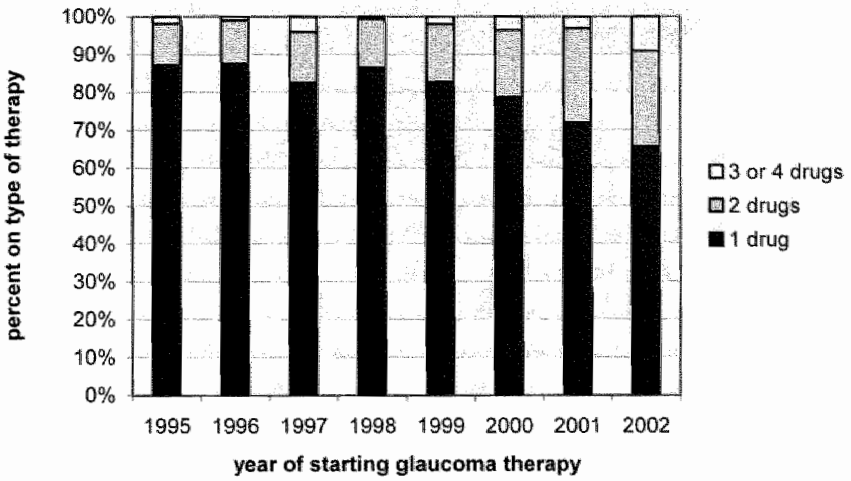
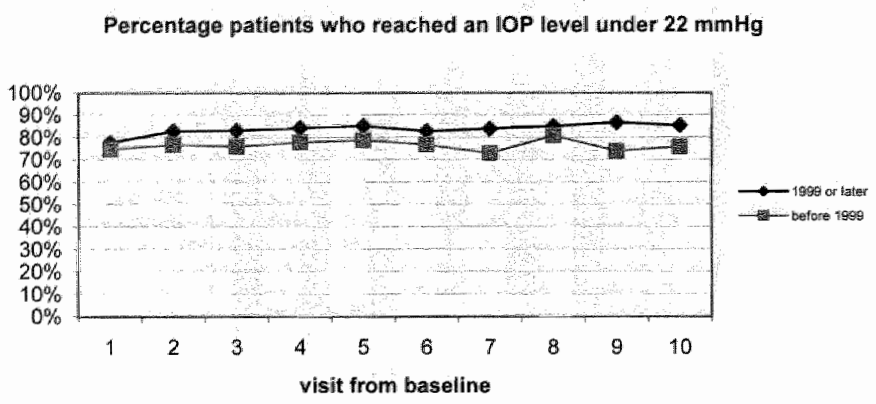


Figure 1. Percent of patients on 1, 2, or 3 or 4 drugs, per year of starting glaucoma therapy from 1995 to 2002, 4 visits after initiation of medical glaucoma therapy

Table 3. IOP before initiating therapy, IOP and mean number of drugs after 4 visits in previously untreated POAG (suspect) and OH patients over the period 1995-2002

	Baseline		4 visits after baseline	
Year of starting	**Mean IOP (± SD) (mmHg)**	**N**	**Mean IOP (± SD) (mmHg)**	**N**
1995	24.8 (± 5.0)	118	18.8 (± 3.4)	117
1996	26.3 (± 5.8)	110	18.8 (± 3.6)	106
1997	25.8 (± 6.0)	152	19.5 (± 3.9)	151
1998	25.6 (± 6.2)	171	19.0 (± 3.8)	169
1999	25.6 (± 6.6)	207	18.4 (± 3.9)	204
2000	26.5 (± 7.4)	233	17.8 (± 4.2)	225
2001	26.1 (± 7.1)	231	17.5 (± 3.8)	199
2002	24.9 (± 6.1)	211	16.9 (± 3.5)	156
Total		1433		1327
P for linear trend	0.85		<0.0001	

A



B

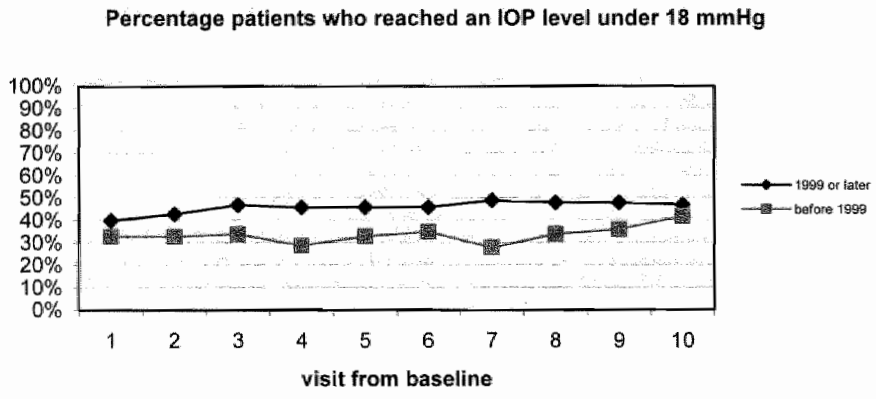


Figure 2. Percent of patients with an IOP level under A. 22 mmHg; or B. 18 mmHg for visits before and after January 1999

Discussion

This multi-center observational study on previously untreated primary open-angle glaucoma (suspect) and ocular hypertension patients shows that after new glaucoma drugs have become available, overall IOP is lower, therapy is changed more often, and patients are treated more intensively. Patients with contraindications to non-selective beta-blockers are more often treated with more potent drugs (hypotensive lipids vs. betaxolol).

We were able to study the long-term effects of the introduction of new glaucoma drugs, and compared the process and outcome of glaucoma treatment between

2 periods. High quality data on comorbidity were available for a large part of the study population (79%).[7] The latter enabled us also to study the process and outcome of glaucoma treatment in patients with contraindications for non-selective beta-blockers.

Although it may be argued that IOP lowering effect of drugs should be compared in randomized clinical trials, an observational study has additional value. Populations studied in randomized clinical trials may be atypical, since those patients tend to differ from patients in the general population in age, general health and severity of the disease.[8-12] An observational study therefore is a better reflection of the situation of everyday practice.[8-10, 12, 13] Moreover, in many situations, the long term effects of the introduction of newer classes of glaucoma medication cannot be studied in a randomized clinical trial for financial and ethical reasons.[14]

The study population consists of patients who were under medical treatment at the time of recruitment. Consequently, glaucoma patients who had undergone glaucoma surgery and had not received glaucoma therapy since then, were not selected. Patients who undergo surgery differ from other glaucoma patients. These patients are more likely to have a high IOP before and after medical treatment, setting the indication for surgery. Since these patients with presumably high IOP were not selected, it may be expected that patients who have started medical treatment years ago, and were included in our study reflect a selected population with lower IOP. However, the mean baseline IOP before January 1999 did not differ from the mean baseline IOP after that date. Moreover, if this selection had occurred, differences in IOP reduction between both periods would have been even larger.

For the purpose of evaluating change of therapy, three moments when the regime could be changed were considered to be sufficient to reach target intraocular pressure in the majority of patients. If visits on a later date had been chosen, the number of patients without data on this visit would have increased.

The more intensive treatment, and the lower IOPs achieved in recent years can be explained by the introduction of new classes of drugs. Because of this, more possibilities for initiating, changing and intensifying therapy for patients in general and for those with insufficient IOP reduction, side effects, or contraindications to beta-blockers had become available.

An additional finding that needs to be discussed is that cardiovascular comorbidity was more often present in the group that started after January 1999 (table 1). A selection bias may be present since patients who had cardiovascular comorbidity a longer time ago, might have died. Another explanation might be that beta-blockers are a relative contraindication for patients with cardiovascular comorbidity. With the introduction of new classes of glaucoma medication more medical treatment options for this group of patients were available, whereas before January 1999, laser treatment or filtration surgery might have been chosen in an earlier stage of the disease.

Patients with glaucoma therapy after January 1999, had more often had a cataract operation than those that initiated glaucoma therapy before this moment. This is in line with observations in the general population where an increase in the number of cataract operations was observed.[15]

With the introduction of new glaucoma medication the number of prescriptions increased, and more classes of glaucoma medications were prescribed, resulting in a decline in the number of glaucoma surgeries, and leading to lower IOPs.[3-6] These outcomes are very likely to be the result of more intensive treatment and more opportunities for treatment when traditional treatment had failed. Our study supports the hypothesis that patients were treated with more potent drugs and treatment was more intense.

In conclusion, this study shows a change in process and improvement in outcome of glaucoma treatment, after new glaucoma drugs had become available.

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7

The impact of a nationwide introduction of new drugs and a treatment protocol for glaucoma on the number of glaucoma surgeries

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Abstract

Purpose: To study the trend in number of glaucoma surgeries, and the influence hereon of the introduction of new glaucoma medication, reimbursement of its costs and the introduction of a treatment protocol.

Methods: Out of the Dutch Health Care Registration, all open-angle glaucoma and ocular hypertension patients aged 20 years and older, who underwent glaucoma surgery were selected. Over the period 1995 until 2003 the trend in the number of monthly performed glaucoma surgeries was described by LOESS spline procedure.

Results: From 1995 until 2003 15,888 surgeries were included. Overall mean age was 67.5 years (SD 13.0). Mean age declined by 0.29 year per year, (95%-CI, 0.21-0.37). In 1995 and 1996 the number of yearly performed glaucoma surgeries was approximately 2400. From 1997 onwards this number started to decrease, resulting in a 45% decrease in the year 2000. From 2000 on the number of surgeries stabilized at approximately 1350 per year. In 1999 the total number of prescriptions rose by 20% compared to 1998, and then stabilized. In 2002 48% of the prescriptions was a prescription for new medication.

Conclusion: The number of glaucoma surgeries in the Netherlands almost halved over a 3.5-year period, most likely due to the introduction of new medications. In the remaining study period the number leveled off. From the present data a substitution effect and not merely a postponement of glaucoma surgeries may be suggested, providing additional evidence that a sustained reduction in the number of glaucoma surgeries was reached in the studied period.

Introduction

New drugs introduce new expectations. New glaucoma drugs have lead to the expectations that in daily practice intraocular pressure (IOP) may now be lowered to a greater extent with fewer and less severe adverse events and that more patients can use these drugs in case of contraindications for or adverse events of other drugs.[1-9] These expectations may be fulfilled if they make glaucoma surgery redundant in some patients. We therefore studied the trend in glaucoma surgeries over the period 1995 until 2003, starting 4 years before and ending 4 years after the reimbursement of the new glaucoma drugs and the introduction of a treatment protocol.

In 1995 topical carbonic-anhydrases inhibitors were introduced in The Netherlands for the treatment of glaucoma and in 1997 prostaglandin analogues and alpha$_2$-selective adrenergic agents became available. It took however, until January 1999 before the Dutch Health Care Insurance Board reimbursed the costs of these new drugs. According to a Dutch law these drugs were to be reimbursed only when used according to a treatment protocol developed by the Dutch Ophthalmologic Society. Hence, while the use of this protocol was not compulsory, the use was strongly reinforced. This treatment protocol was sent to all ophthalmologists in January 1999.[10] The Dutch protocol had great similarities to the guidelines of the European Glaucoma Society developed in 1998.[11] The advice in the Dutch protocol is to start with beta-blocker therapy, and in the presence of contraindications to beta-blockers, to start an other monotherapy. If there is less than 20% reduction in IOP, it is advised to switch to other monotherapy. If there is sufficient IOP reduction but the target IOP is not reached one could either switch to other monotherapy or add another topical therapy. The Dutch protocol provided a list of suitable combinations.

This abrupt change in options and guidelines to treat glaucoma offers the opportunity to study the effect on the occurrence of glaucoma surgeries by investigating the trend in the number of performed glaucoma surgeries.

Methods

Data collection

In the Netherlands, the Dutch Health Care Registration routinely registers data of all hospital discharges and surgical interventions. This registration of diagnosis at discharge is based on the International Classification of Diseases-9 classification (ICD-9). After discharging a patient, the surgeon records medical data on discharge forms. Trained medical coders code these forms afterwards. In case of doubt, medical coders have the possibility to consult either the surgeon or the training center.

The quality of data is ensured by standardization of medical coders and electronic checks on possible errors in data and plausibility of data.

Inconsistencies are immediately reported to the hospital and checked. A further reduction in the amount of errors is reached by monthly evaluation of data and randomly contacting hospitals.

For the present study, data on year of birth, sex, month and year of discharge from the hospital, primary and secondary diagnoses at discharge of the hospital, and primary and secondary glaucoma surgeries were available at an individual patient level. All Dutch general and academic hospitals participate in the registration, these account for 99% of the Dutch hospitals. (Prismant, personal communication).

Subjects

The following surgeries are included in the analysis: trabeculectomy, gonio trepanation, iridencleisis, other scleral fistulizing procedures, cyclodiathermy, cyclocryotherapy, cyclophotocoagulation, trabeculotomy, goniotomy, tube shunt surgery, combined cataract and filtering surgery, cyclodialysis, other specified surgery for lowering IOP and other non specified surgery for lowering IOP.

The patients had to be classified with the following primary and secondary open-angle glaucoma diagnoses (ICD-9 code): preglaucoma, unspecified (365.00), open-angle glaucoma with borderline findings (365.01), ocular hypertension (365.04), open-angle glaucoma, unspecified (365.10), primary open-angle glaucoma (365.11), low tension glaucoma (365.12), pigmentary glaucoma (365.13), pseudoexfoliation glaucoma (365.52), or unspecified glaucoma (365.9).

The codes for secondary glaucomas and for angle closure glaucomas have not been included in the analyses. Except for an age younger than 20 years, no other exclusion criteria were used.

Statistical analysis

The number of glaucoma surgeries per year and per month was calculated for each month and each year from 1995 until 2003. The trend in number of glaucoma surgeries per month was described by the LOESS procedure, using a 0.3 smoother.[12] The SAS (Cary, NC) software was used for performing the LOESS procedure.

Results

From 1995 until 2003 15,888 glaucoma surgeries were performed in patients aged 20 years and older. Forty-eight percent of the patients were male and the mean age was 67.0 years (standard deviation, 13.0 years) (table 1). Mean age declined over the years by 0.29 year per year (95% confidence interval, 0.21 to 0.37). In 1995 and 1996, respectively 2346 and 2434 surgical procedures were performed. From 1997 until the year 2000 the number of yearly-performed surgical procedures decreased to approximately 1300; from then on this

number remained almost constant in 2001, 2002 and 2003 on 1350 surgeries per year. The total number glaucoma surgeries in 2003 showed a decrease of 40% when compared to 1995 (table 1). In figure 1 for sickness fund insured, the total number of prescriptions and the number of prescriptions for new medications are presented. In 1999 the total number of prescriptions for this group rose by 20% compared to 1998, and then stabilized. In 2002 48% of the prescriptions was a prescription for new medication.

Table 1. Number of glaucoma surgeries over the years 1995-2003, mean age ± standard deviation and percentage men

Year	Number of surgeries	Age (mean ± SD)	% Men
1995	2346	68.0 ± 12.5	48.9
1996	2434	67.9 ± 12.7	48.5
1997	2251	68.6 ± 12.8	46.0
1998	1941	68.3 ± 12.9	48.7
1999	1514	67.2 ± 13.5	49.3
2000	1281	66.9 ± 13.6	46.4
2001	1413	66.6 ± 13.4	44.3
2002	1300	66.4 ± 13.3	48.5
2003	1408	65.8 ± 12.9	47.4
Total	15888	67.5 ± 13.0	47.7

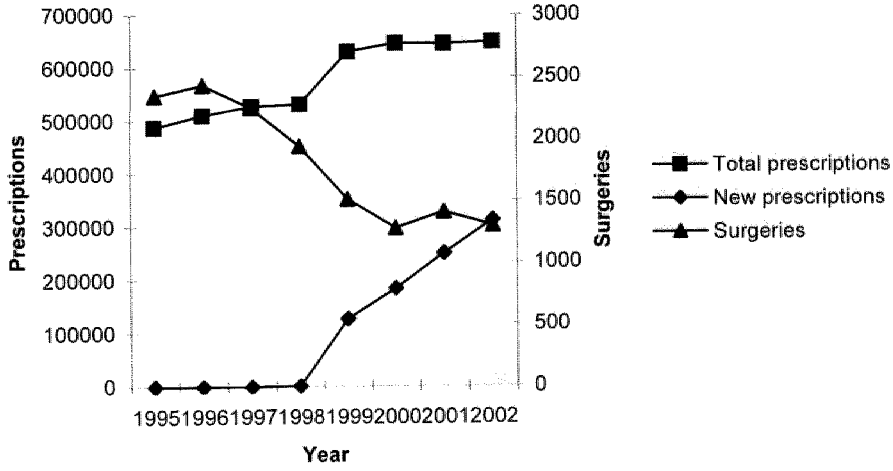

Figure 1. Number of glaucoma surgeries per year from 1995 to 2002, and for sickness fund insured patients the total number of prescriptions and the number of prescriptions for new medication per year from 1995 to 2002

The trend in the number of monthly performed surgical procedures is shown in figure 2. From January 1995 to September 1996 the number of glaucoma surgeries was approximately constant at 200 per month. In the period October 1996 to March 2000 the number of monthly-performed glaucoma surgeries decreased sharply to approximately 110. From April 2000 on, this number leveled off (figure 2). In the period 1997 to 1999 new glaucoma medication and a treatment protocol were introduced, as well as reimbursement of the costs of these new drugs. When stratified by age group, trends were similar among all age groups.

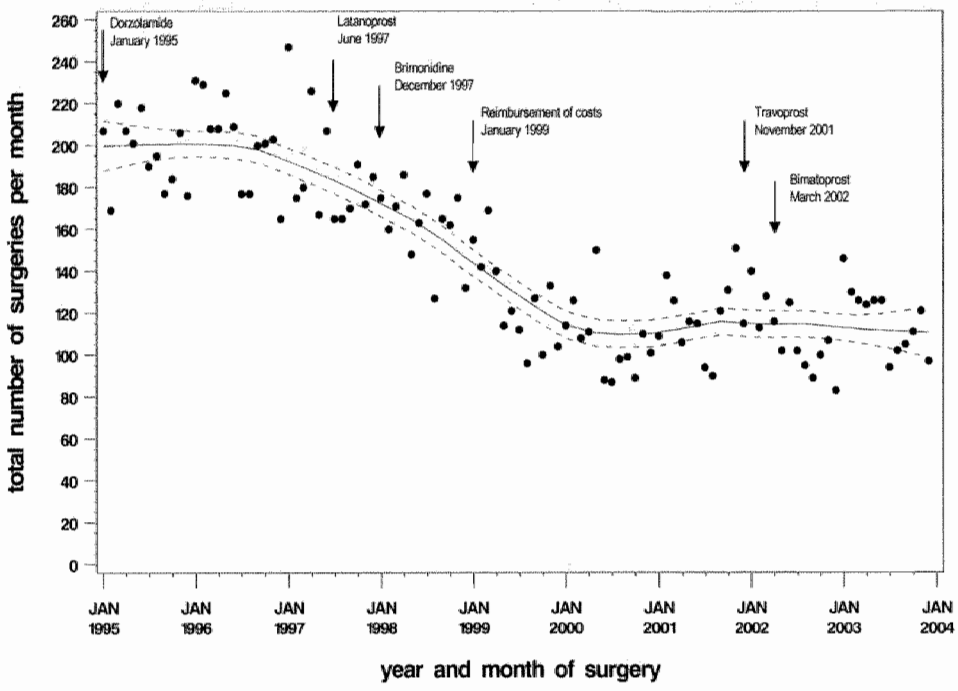

Figure 2. Number of glaucoma surgeries per month from 1995 to 2003 described by LOESS spline procedure. 90%-Confidence bands, moments of introduction of medication and moment of reimbursement of costs

Discussion

From 1997 until 2000, the number of glaucoma surgeries in the Netherlands decreased by 45%. A stabilization was observed in 2001, 2002 and 2003. In the period from 1997 to 1999 new glaucoma drugs, a treatment protocol were introduced, and reimbursement of the costs of these new drugs was agreed on.

Similar to this situation, in 1980 a new opportunity for reducing IOP became available by the introduction of argon laser trabeculoplasty (ALT). A sudden

decrease in number of filtering surgeries was seen, in the period following this introduction. However, this decrease lasted only 2 years after which the number of filtering surgeries in this study returned to previous levels.[13]

One may ask whether the now observed decrease in glaucoma surgeries will last or will turn out to be a temporary effect because of try out of new drugs.

In a study comparable to the present one, Paikal et al[14] observed a downward trend in trabeculectomies in an US Medicare population over the years 1995 to 1998. Strutton and Walt[15] found similar results in an US Medicare population over the years 1994 to 1999. Bateman et al[16, 17] reported similar findings over the years 1994 to 1999 in Scotland. Similar to the present data fewer glaucoma surgeries were performed in the months following introduction of carbonic anhydrases inhibitors, prostaglandin analogues and alpha$_2$ adrenergic agonists. Bateman et al, Strutton and Walt, as well as Paikal et al suggested that the introduction of these medications was at least partly responsible for the downward trend in the number of trabeculectomies.[14-17]

The effectiveness of treatment in glaucoma is judged by monitoring progression of visual field loss. To establish progression of glaucomatous disease, 3 consecutive examinations are often needed.[18] In daily practice this may take a period as long as 2 years. Therefore from the studies of Paikal et al[14], Strutton and Walt[15], and Bateman et al[16, 17] it is impossible to answer the question whether the introduction of new drugs made glaucoma surgeries redundant.

The present investigators analyzed nationwide data over a much longer period after the introduction of new glaucoma medications. Just like in the studies of Paikal et al[14], Strutton[15] and Walt and Bateman et al[16, 17] in The Netherlands, the sudden decrease in the number of glaucoma surgeries was also observed in the period following the introduction of new topical treatments. This indeed, strongly supports the suggestion that the new drugs were responsible for the decreasing number of glaucoma surgeries. From the year 2000 to 2003 the number of surgical procedures remained fairly stable, with the exception of some fluctuations due to the introduction of other drugs similar to the already introduced glaucoma medications. The present observations indicate that in, at least part of, the population glaucoma surgeries have become redundant and were not merely postponed. The declining mean age over the observed years supports this thought (table 1). In case of postponement of glaucoma surgeries a higher mean age in patients who underwent glaucoma surgery would be expected. In the present data similar trends were observed when stratified by age groups. These findings also support the thought that glaucoma surgeries have become redundant and were not merely postponed. Therefore, when surgeries were postponed rather than made redundant, in the higher age groups a rise or at least a smaller decline in number of operations would be expected.

The decrease and leveling off of the number of glaucoma surgeries may be explained by the effects of the new drugs on IOP. The introduction of new medication made medical treatment of glaucoma possible for more patients (eg,

because of lack of effect, side effects or contraindications to existing drugs).[1, 19-21] Furthermore, some of the new drugs generally have to be dosed less frequently[1, 7-9, 22, 23] when compared to the longer existing drugs, this could enhance compliance and thereby better IOP control.[24-28] Also more intensive treatment of glaucoma patients was now possible. The use of these drugs have a direct effect of (at least) postponement of an operation. The use of these drugs was made possible by its reimbursement.

In another study, we evaluated the use of the treatment protocol. A questionnaire was sent to all Dutch ophthalmologists. Of the 295 responding ophthalmologists who treated glaucoma patients, 205 used a protocol for the treatment of glaucoma. Sixty-eight percent used the Dutch protocol, 22% used the almost similar European Glaucoma Society protocol and 8% used an own protocol. Furthermore this study showed that 75% to 95% of the ophthalmologists followed the protocol for at least 80% of the treatment decisions. This study also showed that 62% of the ophthalmologists indicated that the treatment protocol had helped them with the proper indications of these drugs (presented at the Dutch Ophthalmology Society Meeting, Amsterdam, The Netherlands, 2004). Therefore, there is no direct effect of the protocol.

The authors consider the fact that new medication became available is the reason less patients underwent surgery. Reimbursement of the costs of new medication for sickness fund insured people made it possible to prescribe the new medication to a larger group of patients.

Explanations like changes in performed laser trabeculoplasties, surgical capacity, surgical techniques, guidelines about indications for glaucoma surgery, or coding of glaucoma surgeries seem very unlikely, since these changes should have coincided with the fairly sudden decline of the observed performed glaucoma surgeries, which was not the case in the Netherlands.

Angle closure glaucomas were excluded for this study since the management of these types of glaucomas is generally different from the management of open-angle glaucomas. Moreover the treatment protocol focused on the medical treatment of primary open-angle glaucoma, ocular hypertension and low tension glaucoma.

The present study showed a decrease in glaucoma surgeries over a period of 3½ years, and a leveling off in the remaining study period. This suggests a substitution effect and not merely postponement of surgeries. The decrease in number of glaucoma surgeries is most likely due to introduction of new glaucoma drugs. Hereby we have provided additional evidence that a sustained reduction of the number of glaucoma surgeries is reached.

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8

General discussion

Glaucoma is a chronic progressive optic neuropathy that leads to irreversible loss of vision and ultimately to blindness.[1, 2] In the Netherlands approximately 90,000 patients have glaucoma and each year approximately 12,000 new cases are diagnosed.[3] The aim of glaucoma treatment is to reduce further loss of optic nerve tissue, which can be achieved by lowering intraocular pressure with drug treatment, laser or surgery. Several studies have shown that lowering IOP prevents the occurrence and progression of visual field loss.[4-11]

Before 1995, the medical treatment options of glaucoma patients mainly involved beta-blockers, especially timolol. In case of insufficient intraocular pressure (IOP) reduction, side effects, or contra indications, medical alternatives were for example carbonic anhydrases inhibitors and non-selective adrenergic agonists. Severe side effects of the systemic carbonic anhydrases inhibitors led to the development of topical application forms.[12] Allergic reactions to non-selective alpha-adrenergic agonists motivated the research into alpha$_2$-selective adrenergic agonists.[13, 14] It has been known for decades that certain prostaglandins decrease the IOP. Research focused on developing a molecule that sufficiently lowers IOP without simultaneously evoking intolerably severe local adverse reactions.[15, 16] This resulted in the development of hypotensive lipids. Although there were medical alternatives before 1995, for many patients laser treatment was the subsequent option. However, laser treatment is not successful in every patient and the effect is temporary, so in many cases surgery followed.

As expected, in the years following the introduction of new glaucoma drugs, a decline in number of glaucoma operations was observed (figure 1), and the mean IOP of starters on medical therapy was lower compared to the years before the introduction of new glaucoma drugs.

It is likely that these effects are the result of the introduction of new glaucoma drugs, which were expected to be beneficial for the following patients:

- Patients who need to start with glaucoma medication could be started on new drugs. It was expected that these would give more IOP reduction compared to timolol
- Patients who do not respond to a certain medical therapy, could be treated with alternative medical therapy, instead of laser or surgery
- Patients with contraindications to non-selective beta-blockers could be treated with alternative drugs
- Patients with side-effects to certain drugs, could be treated with alternative drugs
- Patients in whom IOP reduction is reached, without side-effects, but who still need a lower IOP, would have more possibilities for additional IOP reduction

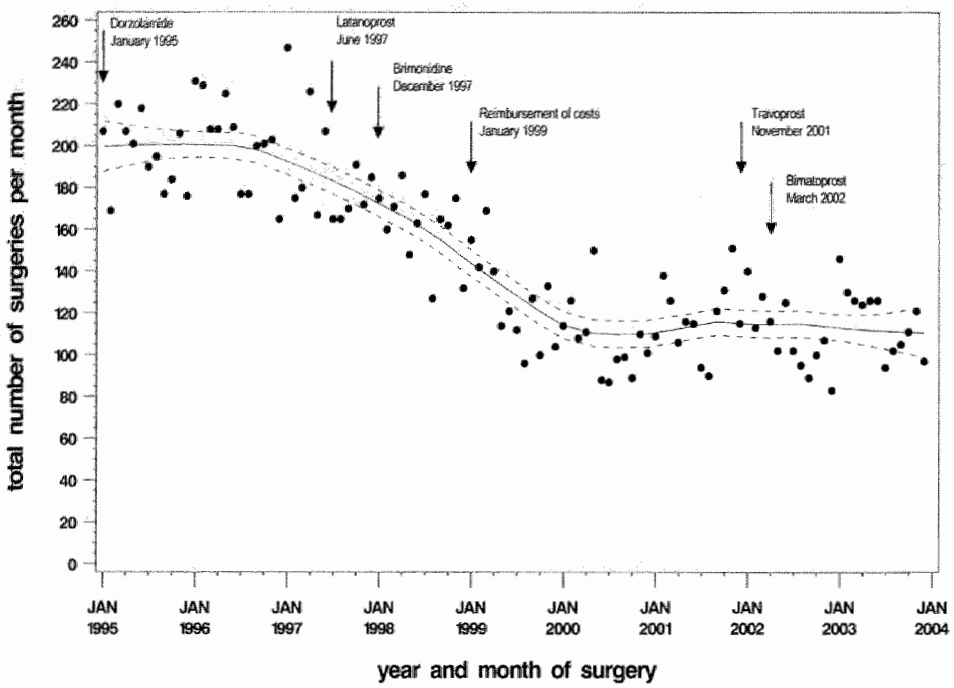

Figure 1. Number of glaucoma surgeries per month from 1995 to 2003 described by LOESS spline procedure. 90%-Confidence bands, moments of introduction of medication and moment of reimbursement of costs

The question can be raised how the new glaucoma drugs had an impact in everyday practice, such that it led to a lower IOP and to a reduction of the number of glaucoma surgeries.

This was investigated by conducting a meta-analysis of randomised clinical trials on the IOP reduction that can be achieved by the most commonly used glaucoma drugs. In this thesis it is shown that timolol and hypotensive lipids are the most potent IOP lowering agents. The evidence comes from a meta-analysis and was further supported by applying a formal statistical test to rank the IOP lowering drugs. This so called network meta-analysis uses direct and indirect comparisons to make a rank order in IOP lowering effects. All commonly used glaucoma drugs and placebo were compared to timolol. Differences between timolol and hypotensive lipids were small, but statistically significant (figure 2).

It is possible that IOP reduction for patients participating in randomised clinical trials differs from the IOP reduction measured in patients in everyday practice.[17-21] Observational research better reflects the latter situation.[17-19, 21, 22] Therefore, an observational study on the IOP reducing effect of timolol and latanoprost was conducted.

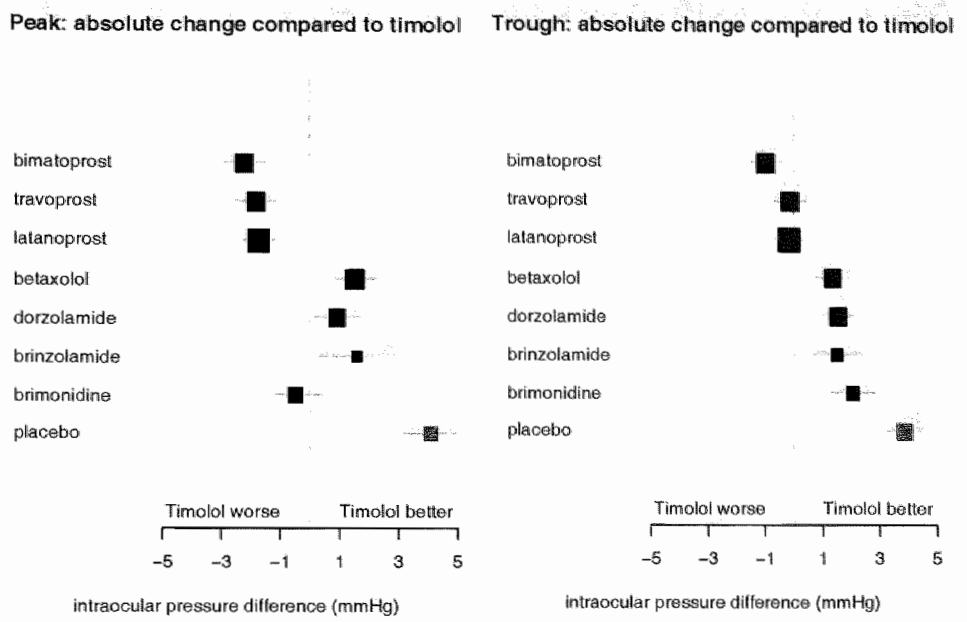

Figure 2. Forest plots of absolute peak and trough IOP reduction reached by starting glaucoma mono therapy, compared to timolol

No difference in IOP lowering between the two agents was found. IOP reductions were similar to those reported in meta-analyses. This further confirms that more influence on IOP in practice can hardly be achieved by changing from timolol to latanoprost. However, in case a patient is not responding to timolol, more alternative monotherapies are now possible. These, like the hypotensive lipids, have a stronger effect compared to some other older alternatives, such as betaxolol.

Another possible explanation for the effect on the IOP might be that selection of patients according to their responsiveness to drugs might have occurred. However, in this thesis we could not identify predicting factors for responsiveness of patients to certain drugs. Thus, selection of patients based on their expected responsiveness to glaucoma drugs was not possible. After starting medical treatment, however, a try out of different monotherapies was possible because of the increased number of treatment options. This leads to consecutive IOP lowering in the follow-up visits when medication is changed to achieve a target pressure.

Randomised clinical trials and observational research indicate that the differences in IOP lowering effects between timolol and hypotensive lipids are small or even absent. Differences between on one hand timolol and hypotensive lipids, and on the other hand betaxolol, brimonidine, and carbonic anhydrases inhibitors were, however, larger. It may be possible that a larger decrease in IOP was achieved, because some of the new drugs are more

potent in reducing IOP than betaxolol which used to be the conventional treatment option in case of contraindications for timolol (figure 2).

Although not extensively discussed in this thesis, it is likely that availability of potent medical alternatives also applies to patients with side effects. The increased number of patients that changed therapy after new glaucoma drugs were introduced supports this hypothesis.

In case additional IOP reduction is needed, in many cases a drug is added to the regime. A meta-analysis on the addition of dorzolamide or latanoprost to timolol monotherapy showed that addition of either agent to timolol leads indeed to additional IOP reduction.

In this thesis it was found that after introduction of new drugs, glaucoma patients received more intensive medical treatment (figure 3).

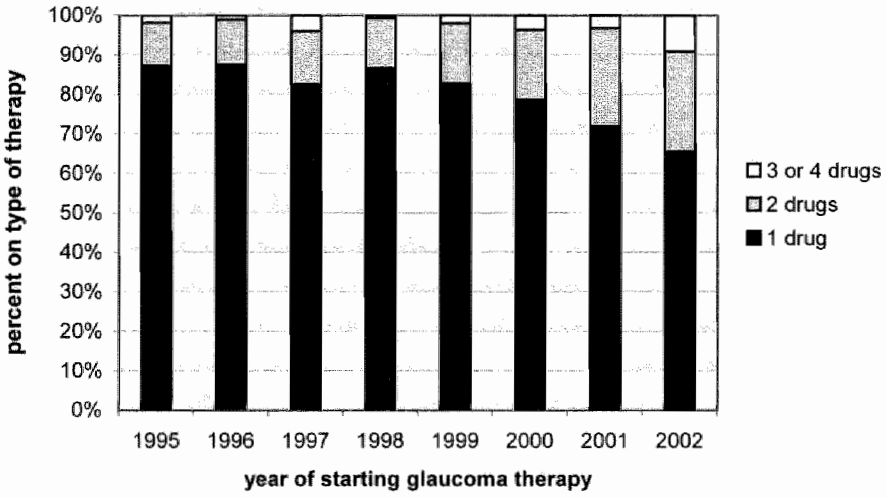

Figure 3. Percent of patients on 1, 2, or 3 or 4 drugs, per year of starting glaucoma therapy from 1995 to 2002, 4 visits after initiation of medical glaucoma therapy

In summary, the results of this thesis show that all types of glaucoma drugs are effective in reducing IOP. When compared to timolol, some new types of glaucoma drugs achieve a similar, a little more IOP reduction, while other new glaucoma drugs are less potent in reducing IOP. For patients who have not responded to previous medical therapy, patients who have contraindications to beta-blockers, patients with side effects, and patients by whom earlier treatment is well tolerated, the drug led to IOP reduction but who still need additional IOP reduction, the new glaucoma drugs are a valuable addition to the glaucoma treatment options. This increase of medical treatment options has led to a higher percentage of patients in whom a lower IOP was achieved (figure 4), and

to a reduction in the number of glaucoma surgeries (figure 1). Thus, while the conventionally available drugs remain valuable, the clinical application of new glaucoma drugs, that were introduced based on IOP lowering in clinical trials, has led to improvements in care for glaucoma patients.

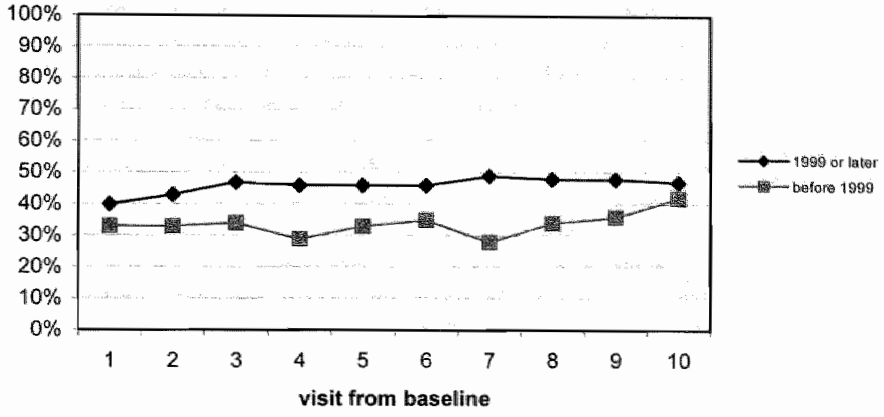

Figure 4. Percent of patients with an IOP level lower than 18 mmHg for visits before and after January 1999

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Summary

Glaucoma is one of the leading causes of visual impairment worldwide and ultimately can result in blindness. The most important risk factors for glaucoma are elevated intraocular pressure (IOP), a positive family history of glaucoma, age and African descent. Treatment of this chronic progressive optic neuropathy mainly involves reduction of the intraocular pressure in order to prevent (further) visual field loss. IOP reduction can be achieved by drugs, laser and surgery.

Since 1995 several new glaucoma drugs have been introduced. These new drugs are topical carbonic anhydrasis inhibitors, alpha$_2$-adrenergic agonists, prostaglandin analogues and prostamides. In the Netherlands, the costs of these new drugs are reimbursed for sick-fund insured patients since January 1999. This implied that from that moment on the new glaucoma drugs had become available to the entire Dutch population. At the same time a treatment protocol for glaucoma was adapted and distributed to all Dutch ophthalmologists. In the protocol it was advised to start treatment with non selective beta-blocker monotherapy. In case of contraindications to this type of beta-blocker, the advice was to start with monotherapy of the selective beta-blocker betaxolol or any of the newly introduced drugs.

The studies described in this thesis were carried out within the framework of the DUtch Research project on outcome and treatment IN Glaucoma patients (DURING study).

In **chapter 2** by using meta-analysis of randomized clinical trials the pooled 1-month absolute and relative change in IOP from baseline of all commonly used glaucoma drugs was calculated. In total 28 randomized clinical trials were included. These articles reported of 6,953 participants for trough and 6,841 for peak. Relative IOP reductions at peak ranged from 33% for bimatoprost to 17% for brinzolamide, at trough the range was from 29% (travoprost) to 17% (dorzolamide, brinzolamide). Placebo reduced IOP by 5% at both peak and trough. The difference in absolute IOP reduction from baseline between timolol and prostaglandin analogues or prostamide varied from -0.4 to 0.1 mmHg at trough and from 1.0 to 1.5 mmHg at peak. This meta-analysis suggests bimatoprost, travoprost, latanoprost and timolol are the most effective IOP reducing agents in primary open angle glaucoma and ocular hypertension patients.

Chapter 3 presents a rank order in IOP reducing effects. This rank order is calculated by network meta-analysis with the data used in chapter 2. Network meta-analysis takes into account direct as well as indirect evidence and performs a formal statistical test on differences in IOP reduction. This study shows that all drugs statistically significantly differ from placebo in lowering IOP. At peak moment the rank order from high to low in achieved mean IOP reduction is bimatoprost, travoprost and latanoprost, brimonidine, timolol, dorzolamide, betaxolol, brinzolamide. At trough moment this rank order is bimatoprost, latanoprost, travoprost, timolol, betaxolol, dorzolamide, brinzolamide, brimonidine. At peak, bimatoprost, travoprost and latanoprost reduce IOP significantly more than timolol, the absolute difference is 1.7 to 2.2

mmHg. At trough, bimatoprost is the only drug that reduced IOP significantly more than timolol, this absolute difference is 1 mmHg. Timolol reduced IOP statistically significant more than betaxolol, dorzolamide, and brinzolamide.When additional IOP reduction is necessary, glaucoma drugs can be combined. This can be done as concomitant use of two drugs or as a fixed combination. **Chapter 4** presents a meta-analysis in which the IOP reducing effects of adding dorzolamide or latanoprost to timolol monotherapy are calculated. The overall pooled change from baseline for dorzolamide added to timolol irrespective of concomitant or fixed use was 16% (3.9 mmHg) at trough 20% (4.9 mmHg) at peak. The concomitant use of latanoprost and timolol after a run-in on timolol, gave a pooled change from baseline of 27% (6.0 mmHg) at the mean diurnal curve. Treatment with the fixed combination after a run-in on timolol resulted in a mean reduction of 13% (3.0 mmHg) at the mean diurnal curve. Adding either dorzolamide or latanoprost to timolol led to a substantial additional decrease in IOP. However, due to the inclusion of patients with high untreated IOP and patients who are less responsive to timolol the exact magnitude of the decrease and the patients to whom it applies remain obscure.

For several reasons achieved IOP reduction may differ between clinical practice and more controlled studies. Patients who participate in randomized clinical trials tend to be younger, have better health and have better compliance. Therefore in **chapter 5** IOP reductions reached in clinical practice with timolol and latanoprost were studied. Indications, contraindications and risk factors, were taken into account to study whether intraocular pressure reduction could be predicted from these variables. 156 subjects started on timolol and 76 started on latanoprost monotherapy. Mean relative change was 27% for both timolol and latanoprost. No significant difference in intraocular pressure reduction between timolol and latanoprost was found when adjusting for indications, contraindications, and risk factors. In clinical practice timolol and latanoprost achieve similar IOP reductions. These reductions are comparable to those achieved in randomized trials. Except IOP at baseline, no clinically relevant information for glaucoma management could be used to predict IOP reduction accurately.

Differences in IOP lowering effect between the most potent new glaucoma drugs and the conventional drug timolol are small in randomized clinical trials and absent in clinical practice. However, the value of new drugs cannot always be assessed by comparing them in randomized clinical trials. Therefore, in **chapter 6** changes in process and outcome of glaucoma treatment 4 years before (1995-1998) and 4 years after (1999-2002) new glaucoma drugs became available are described. Of the total of 1561 patients, 551 started before new glaucoma drugs became available. In the years after new medication became available a shift from starting on betaxolol and non-selective beta-blockers other than timolol to prostaglandin analogues took place. This shift was more pronounced in patients with respiratory comorbidity. The percentage of prescriptions for timolol did not differ between both periods.

In the period 1999-2002 patients changed more often from therapy compared to the period 1995-1998 (38% vs. 27%, $p<0.0001$). In recent years, glaucoma

patients are treated more often with two or more drugs. In the period 1995-2002, baseline IOP did not differ over the years, whereas the mean IOP after treatment trended to lower pressures in recent years ($p<0.0001$). After new drugs became available more patients reached IOP under a certain level (22 and 18 mmHg) than before this moment, 85% vs. 77%, and 46% vs. 33% respectively ($p<0.0001$). This study shows a change in process and an improvement in outcome of glaucoma treatment after the general availability of new glaucoma drugs.

The trend in number of glaucoma surgeries, and the influence of the introduction of new glaucoma medication, reimbursement of its costs and the introduction of a treatment protocol were studied in **chapter 7**. Data obtained from the Dutch Health Care Registration were used to calculate the trend in the number of monthly performed glaucoma surgeries over the period 1995 until 2003. In total, 15.888 surgeries were included. In 1995 and 1996 the number of yearly performed glaucoma surgeries was approximately 2400. From 1997 onwards this number started to decrease, resulting in a 45% decrease in the year 2000. From 2000 on the number of surgeries stabilized at approximately 1350 per year. In 1999 the total number of prescriptions rose by 20% compared to 1998, and then stabilized. In 2002 48% of the prescriptions was a prescription for new medication. The results of this study suggest a substitution effect and not merely a postponement of glaucoma surgeries.

In **chapter 8** the findings described in this thesis are discussed. This thesis shows that while the conventionally available drugs remain valuable, the clinical application of new glaucoma drugs that were introduced based on IOP lowering in clinical trials has led to improvements in care for glaucoma patients.

Samenvatting

Glaucoom is één van de meest voorkomende oorzaken van achteruitgang van het gezichtsvermogen en kan tot blindheid leiden. De belangrijkste risicofactoren voor glaucoom zijn: verhoogde oogdruk, familiaire aanleg voor glaucoom, leeftijd en Afrikaanse afkomst. De behandeling van glaucoom is gericht op het voorkomen van verder verlies van gezichtsvermogen door het verlagen van de oogdruk met medicijnen, laserbehandeling of een chirurgische ingreep.

Vanaf 1995 zijn er nieuwe glaucoommiddelen geïntroduceerd: topicale carbo-anhydrase remmers, alpha$_2$-adrenerge agonisten, prostaglandine analogen en prostamides. Vanaf 1999 worden de kosten van deze nieuwe middelen ook voor ziekenfondspatiënten vergoed. Hierdoor ontstond voor alle Nederlandse glaucoompatiënten de mogelijkheid om met deze nieuwe middelen behandeld te worden. Tegelijkertijd met de vergoeding van de kosten werd een behandelprotocol voor glaucoom geïntroduceerd en verspreid onder de Nederlandse oogartsen. In dit protocol werd geadviseerd om met monotherapie van een niet selectieve bètablokker te starten. Voor behandeling van patiënten met contra-indicaties voor dit type bètablokkers, luidde het advies om met monotherapie van de selectieve bètablokker betaxolol of met één van de nieuwe middelen te beginnen.

De studies die beschreven zijn in dit proefschrift zijn uitgevoerd als onderdeel van "the DUtch Research project on outcome and treatment IN Glaucoma patients" (DURING studie).

In **hoofdstuk 2** is met een meta-analyse van gerandomiseerde klinische studies de absolute en relatieve oogdrukdaling na 1 maand monotherapie berekend. In totaal zijn 28 trials geïncludeerd die de meest voorgeschreven glaucoommiddelen hebben bestudeerd. Voor het piekmoment waren gegevens van 6.953 patiënten beschikbaar en voor het dalmoment van 6.841 patiënten. De relatieve oogdrukdalingen varieerden van 33% voor bimatoprost tot 17% voor brinzolamide op het piekmoment. Op het dalmoment was dit van 29% (travoprost) tot 17% (dorzolamide, brinzolamide). Met placebo werd een oogdruk verlagend effect van 5% gevonden op zowel het piek- als dalmoment. Het absolute verschil in oogdrukdaling tussen timolol en de prostaglandine analogen of prostamide varieerde van -0,4 tot 0,1 mm Hg op het dalmoment, en van 1,0 tot 1,5 mm Hg op het piekmoment. De resultaten van deze meta-analyse suggereren dat bimatoprost, travoprost, latanoprost en timolol de meest effectieve oogdrukverlagende middelen zijn voor patiënten met primair open kamerhoek glaucoom of oculaire hypertensie.

In **hoofdstuk 3** zijn met een netwerk meta-analyse de meest gebruikte glaucoommiddelen geordend naar oogdrukverlagend effect. Voor deze analyse is gebruik gemaakt van de gegevens van hoofdstuk 2. In een netwerk meta-analyse worden zowel directe als indirecte vergelijkingen gebruikt om met een formele statistische toets verschillen in oogdruk verlagend effect tussen middelen te berekenen. Alle bestudeerde glaucoommiddelen verlagen de oogdruk statistisch significant meer dan placebo. De volgorde van het meest naar het minst krachtige oogdrukverlagende middel op het piekmoment is

bimatoprost, travoprost and latanoprost, brimonidine, timolol, dorzolamide, betaxolol, brinzolamide. Op het dalmoment is deze volgorde: bimatoprost, latanoprost, travoprost, timolol, betaxolol, dorzolamide, brinzolamide, brimonidine. Op het piekmoment verlagen bimatoprost, travoprost and latanoprost de oogdruk significant meer dan timolol, het absolute verschil is 1,7 tot 2,2 mm Hg. Op het dalmoment was bimatoprost het enige middel waarmee een statistisch significant sterkere oogdrukdaling werd bereikt dan timolol, het absolute verschil tussen beide middelen is 1 mm Hg. Op zowel het piek- als dalmoment verlaagt timolol de oogdruk statistisch significant meer dan betaxolol, dorzolamide en brinzolamide.

Naast het gebruik als monotherapie kunnen glaucoommiddelen gecombineerd worden om additionele oogdrukdaling te geven. Deze combinatietherapie kan gegeven worden als twee losse middelen, maar ook in de vorm van een gefixeerd preparaat. In **hoofdstuk 4** worden de resultaten van een meta-analyse naar de oogdruk verlagende effecten van het toevoegen van latanoprost of dorzolamide aan timolol monotherapie besproken. De extra daling die werd bereikt met het toevoegen van dorzolamide was 16% (3,9 mmHg) op het dal- en 20% (4,9 mmHg) op het piekmoment. De oogdrukdaling die werd bereikt met de losse en de gefixeerde combinatie was vergelijkbaar. Met het toevoegen van latanoprost aan timolol werd een extra daling van de oogdruk dagcurve van 27% (6,0 mmHg) gevonden. Met de gefixeerde combinatie van deze middelen in plaats van timolol monotherapie was deze extra daling 13% (3,0 mmHg). Uit dit hoofdstuk blijkt dat zowel het toevoegen van dorzolamide als het toevoegen van latanoprost aan monotherapie van timolol leidt tot een additionele daling van de oogdruk. Vanwege de inclusie van patiënten met een hoge onbehandelde oogdruk en patiënten die een verminderde respons op timolol geven is de exacte grootte van de oogdrukdaling onbekend voor elk van deze groepen patiënten afzonderlijk.

Er zijn meerdere redenen waarom resultaten van gerandomiseerde klinische studies kunnen verschillen van studies die zijn uitgevoerd in de dagelijkse praktijk. De patiënten die deelnemen aan klinische studies zijn in veel gevallen jonger, gezonder en hebben een betere therapietrouw. In **hoofdstuk 5** zijn daarom de oogdrukdalingen van latanoprost en timolol monotherapie in de praktijk bestudeerd. Tevens is gekeken of het mogelijk is om deze daling te voorspellen aan de hand van indicaties, contra-indicaties en risicofactoren voor glaucoom. In deze studie startten 156 patiënten met timolol en 76 met latanoprost monotherapie. Voor zowel timolol als latanoprost was de relatieve oogdrukdaling 27%. Deze daling komt overeen met de daling die in gerandomiseerde klinische studies gevonden wordt. Ook na correctie voor indicaties, contra-indicaties en risicofactoren werd geen verschil in oogdrukdaling tussen timolol en latanoprost gevonden. Behalve met de variabele "oogdruk vóór start van behandeling", kon met behulp van geen van de geëvalueerde variabelen die beschikbaar zijn voor de oogarts voor de behandeling van glaucoom, de mate van oogdrukdaling goed voorspeld worden.

Uit de voorgaande hoofdstukken blijkt dat de verschillen in bereikte oogdrukdaling tussen het conventionele medicijn timolol en de meest effectieve

nieuwe medicijnen klein zijn in gerandomiseerde trials, en afwezig in de dagelijkse praktijk. De waarde van nieuwe middelen kan echter niet alleen geëvalueerd worden op basis van oogdrukdalingen gemeten in gerandomiseerde studies. Daarom worden in **hoofdstuk 6** de veranderingen in het proces en de uitkomst van glaucoom behandeling besproken sinds de vergoeding van nieuwe middelen en introductie van het behandelprotocol. Voor deze studie zijn patiënten geselecteerd die in de 4 jaar voordat de nieuwe middelen voor iedereen in Nederland beschikbaar waren (n=551) (1995-1998) en 4 jaar na dit moment (n=1510) (1999-2002) gestart zijn met glaucoom medicatie. De jaren nadat de nieuwe middelen beschikbaar waren trad er een verschuiving van betaxolol en niet-selectieve bètablokkers anders dan timolol naar prostaglandines op. Deze verschuiving was sterker aanwezig in de groep patiënten met respiratoire co-morbiditeit. Het percentage voorschriften voor timolol verschilde niet tussen beide perioden.

In de periode 1999-2002 veranderden meer patiënten van medicatie tijdens hun 1^e of 2^e bezoek vergeleken met de jaren ervoor (38% vs. 27%, p>0,0001). In recente jaren is er vaker behandeld met 2 of meer medicijnen dan voorheen. Over de periode 1995-2002 was een dalende trend in gemiddelde oogdruk te zien (p<0.0001), terwijl de begindruk niet veranderde. In de jaren nadat nieuwe medicatie beschikbaar kwam werd statistisch significant vaker een oogdruk onder een zekere grens (22 of 18 mmHg) bereikt in vergelijking met de jaren ervoor. Deze percentages waren respectievelijk 85% vs. 77% en 46% vs. 33%. Dit hoofdstuk laat zien dat er sinds de introductie van nieuwe glaucoommiddelen een verandering in het proces van glaucoombehandeling is opgetreden en dat de uitkomst met betrekking tot oogdrukdaling verbeterd is.

De trend van het aantal glaucoomoperaties en de invloed hierop van introductie van nieuwe medicatie, vergoeding van de kosten en de introductie van een behandelprotocol is bestudeerd in **hoofdstuk 7**. Gegevens van de landelijke medische registratie (LMR) zijn gebruikt om de trend van het aantal glaucoom operaties per maand van 1995-2003 te berekenen. In totaal zijn er 15.888 operaties geïncludeerd. In 1995 en 1996 werden jaarlijks zo'n 2400 glaucoom operaties verricht. Vanaf 1997 begon het aantal operaties te dalen, in 2000 was deze daling 45% ten opzichte van 1997. Vanaf 2000 stabiliseerde het aantal operaties op 1350 per jaar. Het aantal voorschriften voor glaucoommedicatie steeg in 1999 met 20% ten opzichte van 1998 en stabiliseerde in de jaren na 1999. In 2002 was 48% van alle voorschriften een voorschrift voor nieuwe medicatie. De resultaten van dit hoofdstuk suggereren dat er voornamelijk vervanging van operaties door medicamenteuze behandeling heeft plaatsgevonden en niet zo zeer uitstel van operaties.

In **hoofdstuk 8** worden bevindingen van dit proefschrift bediscussieerd. Dit proefschrift laat zien dat de klinische toepassing van nieuwe middelen, die geïntroduceerd zijn op basis van oogdrukverlaging in klinische trials, heeft geleid tot verbeterende zorg voor glaucoompatiënten, maar dat de conventionele middelen waardevolle opties blijven voor de behandeling van glaucoom.

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Rikkert van der Valk
Maastricht, oktober 2005

Curriculum Vitae

Rikkert van der Valk was born on April 5, 1977 in 's Gravenhage, The Netherlands. After completing secondary school (VWO) in 1995 at the Montessori Lyceum Herman Jordan in Zeist, he studied Human Nutrition and Epidemiology at Wageningen University (M.Sc.). As part of the training he fulfilled three traineeships, two at the department of Human Nutrition and Epidemiology at Wageningen University. The third training period he spend at the African Medical and Research Foundation in Kibwezi, Kenya. He graduated in 2000. For the combined traineeships in Wageningen and Kenya he obtained a qualification as "Epidemiologist A" in 2000.

From 2001 until 2005 Rikkert van der Valk worked as a researcher at the department of Epidemiology of the University of Maastricht and the department of Ophthalmology of Maastricht University Hospital. He conducted research on glaucoma medication; which is presented in this thesis. He presented the results at several national and international meetings and conferences. In 2005 Rikkert van der Valk was qualified to enter Medicine at the School for Utrecht Medical Masters of Utrecht University. In February 2006 he will start this education.